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NanoRiskCat – A Conceptual Decision Support Tool for Nanomaterials

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Preface

The Danish Environmental Protection Agency (DEPA) has previously initiated projects which have highlighted the nanomaterials that can be found in products on the Danish market (Consumer Project No. 81), and the nanomaterials used in the Danish industry (Environmental Project No. 1206).

As a follow-up on these reports, the DEPA identified a need to try to develop a concept that can provide support to companies and regulators in regard to assessing, ranking and communicating what they know about the risks of nanomaterials in specific uses in products.

DEPA has therefore initiated this project in order to examine the possibilities for developing such a conceptual framework for screening of potential environmental and health risks for nanomaterials used in products. DEPA contracted with DTU Environment in collaboration with the National Research Centre for the Working Environment to carry out this task.

The current project is one of the initiatives under the national action plan for Chemicals which also includes a survey on basic knowledge about exposure and potential environmental and health risks for selected nanomaterials (Environmental Project) and on carbon nanotubes (Environmental Project).

The study has been guided by a steering group consisting of Flemming Ingerslev and Poul Bo Larsen (Danish Environmental Protection Agency), Poul-Erik Andersen (The Danish Working Environment Authority), Ulla Vogel (DTU Food/ National Research Centre for the Working Environment), and Stig I. Olsen (DTU Management)

This report was prepared by Steffen Foss Hansen (DTU Environment), Anders Baun (DTU Environment), and Keld Alstrup Jensen (National Research Centre for the Working Environment) during a period from January 2010 to May 2011.

Please note that the publication of this report does not signify that the content necessarily reflects the view of the Danish EPA.

Danish Environmental Protection Agency, November 2011

Dansk Sammenfatning

Nanomaterialer bliver anvendt i et hastigt stigende antal produkter til gavn for såvel virksomheder som private forbrugere. Antallet af mulige nanomaterialer er ubegrænsede og de forbedrede materialeegenskaber, der opnås på grund af nano-størrelsen muliggør brug i vidt forskellige produkter. I løbet af det sidste årti er der, samtidigt med udviklingen af nanoteknologien, sat fokus på de mulige miljø- og sundhedsskadelige egenskaber af nogle typer af nanomaterialer.

På den baggrund har Miljøstyrelsen identificeret et behov for at undersøge mulighederne for at udvikle et nyt vurderings-koncept, som kan yde støtte til virksomheder og myndigheder i forbindelse med vurdering, rangordning og formidling viden om af hvad de ved om mulige risici af nanomaterialer i specifikke produktanvendelser. Risiko forstås i denne sammenhæng som en kombination af 1) muligheden for eksponering af nanomaterialet gennem den specifikke anvendelse og 2) muligheden for at der kan ske en negativ påvirkning af menneskelig sundhed eller miljøets organismer.

Gennem dette projekt har DTU Miljø og Det Nationale Forskningscenter for Arbejdsmiljø igangsat udviklingen af et konceptuelt screeningsværktøj, NanoRiskCat (NRC), med det formål at muliggøre en identifikation, kategorisering og rangordning af eksponering og effekter af nanomaterialer, der anvendes i forbrugerprodukter. NanoRiskCat er baseret på data til rådighed i peer-reviewed videnskabelige litteratur og andre former for reguleringsmæssigt relevante kilder.

Fokus for NRC er på anvendelse og udsættelse for nanomaterialer i forbindelse med professionelle brugere, private forbrugere, samt miljømæssige udledning. Det er håbet, at NanoRiskCat kan og vil hjælpe producenter, brugere, regulerende myndigheder, og andre interessenter med at vurdere, kategorisere, rangordne og kommunikere den nuværende viden om potentialet for eksponering og effekter af nanomaterialer. Dette er forsøgt gjort gennem en generisk velstruktureret skabelon, hvor de specifikke anvendelser af et givet nanomateriale rapporteres og vurderes. Helt konkret gøres dette i NRC ved at fastsætte detaljerede retningslinjer for kortlægning og indberetning af:

1. Eksponeringspotentiale for professionelle slutbrugere
2. Eksponeringspotentiale for forbrugerne
3. Eksponeringspotentiale for miljøet
4. En foreløbig farlighedsevaluering for mennesker
5. En foreløbig farlighedsevaluering for miljøet

En generisk skabelon for kortlægning og rapportering af disse fem punkter for en bestemt anvendelse af et nanomateriale er udviklet og kan findes i bilag 1 til denne rapport.

Resultatet af en produkt-screening med NanoRiskCat kommunikeres i form af: en kort titel, der beskriver brugen af nanomateriale og en farvekode, der består af fem punkter (f.eks. ●●●|●●). De første tre farvede prikker henviser altid til den potentielle eksponering af professionelle brugere, forbrugere og miljøet i den pågældende rækkefølge, mens de sidste to farvede prikker altid henviser til alvorligheden af de mulige fareegenskaber for henholdsvis mennesker og miljø. Farverne specificerer om den angivne eksponering og de angivne effekter vurderes til at være høj (rød), medium (gul), lav (grøn) eller ukendt (grå).

Farvekodningen af de første tre prikker, der repræsenterer eksponeringspotentialet, er baseret på de generiske proces- og produktkategorier der anvendes ved opbygning og beskrivelse af eksponeingsscenarier i REACH og som er angivet i de relevante guidance dokumenter det Europæiske Kemikalieagentur (ECHA) har udgivet[1]. Hver proceskategori- og produktkategori har i dette projekt fået tildelt en farvekode (●,●,● eller ●) baseret på 1) placeringen af nanomaterialet (bulk, overflade, væske, luftbåret, osv.) og 2) en vurdering af nanomaterialets eksponeringspotentiale baseret på den beskrivelse af de enkelte processer, produktkategorier, tekniske funktioner, artikler og miljømæssige frigivelseskategorier, som forefindes i REACH vejledningen.

Ved farvekodningen af fjerde prik, som repræsenterer de potentielle sundhedsfarer i forbindelse med anvendelsen af en given nanomateriale, bør følgende indikatorer overvejes:

1. Opfylder ***nanomaterialet*** HARN[2]-paradigmet?

2. Er ***bulk-formen*** af nanomaterialet kendt for at forårsage eller kunne medføre alvorlige skadelige effekter, dvs. er bulk formen klassificeret i kategori 1 eller 2 i henhold til CLP[3] med hensyn til en eller flere alvorlige sundhedsmæssige effekter såsom fx mutagenicitet, kræft eller reproduktionstoksicitet?

3. Er ***bulk-formen*** af nanomaterialet klassificeret for andre, mindre alvorlige sundhedsmæssige effekter i henhold til CLP?

4. Er det specifikke ***nanomateriale*** kendt for at være akut giftigt?

5. Er der tegn på, at ***nanomaterialet*** kan forårsage skadelige effekter såsom genotoksicitet, mutagenicitet, kræft, luftvejs- og hjertekarsygdomme,

[1] ECHA 2010 Guidance on information requirements and chemical safety assessment Chapter R.12: Use descriptor system Version 2. Tilgængelig: http://guidance.echa.europa.eu/docs/guidance_document/information_requirements_r12_en.pdf (Besøgt: 25-11-2011)

[2] HARN refererer til High Aspect Ratio Nanopartikler. For at nanopartikler opfylder HARN skal nanopartiklerne have en længde/diameter aspect ratio større end 10 til 1. Desuden kræves det, at: 1) Diameteren af fibrene skal være tynd nok til at passere cilierede luftveje, 2) længden skal være lang nok til at indlede begyndelsen af fx frustrerede fagocytose og anden inflammatoriske respons, og 3) de nanomaterialer skal være biopersistent (Tran et al 2008).

[3] Europa-Parlamentets og Rådets Forordning (EF) Nr. 1272/2008 af 16. december 2008 om klassificering, mærkning og emballering af stoffer og blandinger og om ændring og ophævelse af direktiv 67/548/EØF og 1999/45/EF og om ændring af forordning (EF) nr. 1907/2006

neurotoksiske eller reproduktionsskadelige effekter i mennesker og/ eller laboratoriedyr, eller er der dokumenteret en organspecifik ophobning?

De CLP klassificeringer, der allerede findes på bulk formen af materialet med hensyn til menneskelig sundhed bruges i NanoRiskCat som udgangspunkt for at etablere et minimum niveau for den toksikologiske profil af nanoformen. Principielt antages det, at oplysninger om bulk formen af materialet kan anvendes under den antagelse, at de toksikologiske og økotoksikologiske virkninger af nanomatetialet er lig med eller mere udtalt / alvorlig i forhold til bulk formen. Således kan fareoplysninger om bulk formen af materialet danne grundlag for fastlæggelsen af det laveste bekymringsniveau der bør indtages med hensyn til nanomaterialet.

Miljøfarelighedsvurderingen ved anvendelsen af et givent nanomateriale (prik fem) bør omfatte overvejelser om hvorvidt nanomaterialet er:

1. Farligt for organismer i miljøet?
2. Persistent?
3. Bioakkumulerende?
4. Fører til irreversible skader på miljøet (fx økosystem virkninger)?
5. Mobilt?
6. Nyt eller unikt?

Det er vigtigt at bemærke, at NanoRiskCat beskriver en trinvis proces i den forstand, at når en farvekode er blevet givet afsluttes processen. Dvs. hvis der fx er nok information til at give en rød farvekode pga. CLP klassificeringen af bulk formen af materialet så stopper processen.

For at hjælpe brugerne af NRC med at kommunikere den videnskabelige begrundelse for tildelingen af en farvekodning for sundheds- og miljøfarekategoriseringen, er en række standardsætninger blevet udviklet. Disse sætninger er beregnet til at afspejle primært om kategoriseringen er baseret på ***in vivo*** eller ***in vitro*** undersøgelser og med hensyn til hvilke effekter. Afhængigt til den endelige sundheds- og miljøfarekategorisering, skal brugeren af NRC vælge den af disse standardsætninger, der bedst afspejler det videnskabelige grundlag for at tildelte farvekoden.

For at illustrere anvendeligheden af NanoRiskCat er to eksempler blevet gennemført. Det ene er for C60-fullerener anvendt i et smøremiddel, mens det anden er nanoTiO_2 anvendt i solcreme. Disse to eksempler, som er udvalgt til brug for udviklingen af konceptet, men de er også medtaget i den aktuelle rapport for at at belyse mulighederne for at anvende NanoRiskCat. NanoRiskCat-koden for C60 i smøremidlet er ●●●|●● eftersom eksponeringspotentialet vurderes at være højt for professionelle slutbrugere, forbrugere og miljøet. Den potentielle sundhedsfare vurderes til at være medium (dvs. gul) baseret på ***in vitro*** data, der indikerer, at der er mindst én sundhedsskadelig effekt associeret med C60, mens den potentielle miljøfare er vurderet til at være høj (dvs. rød) baseret på flere studier, der indikerer at C60 kan forårsage letale og subletale effekter på fisk og krebsdyr ved koncentrationer < 10 mg/l. For TiO_2 i solcreme var NanoRiskCat koden ●●●|●●, da eksponeringspotentialet vurderes at være højt (dvs. rød) for

res at være højt (dvs. rød) for professionelle slutburgere, forbrugere og miljøet. Potentialet for sundhedsfarlighed af TiO_2 vurderes til at være højt (dvs. rød) baseret på ***in vitro*** data, som tyder på at nanoformen af TiO2 forårsager mindst en sundhedsskadelig effekt. På miljø-effektsiden, blev potentialet for TiO_2 også vurderet som højt, på basis af et konkret studie med dafnier, hvor den 50% af dyrene døde ved eksponering af 2 mg/L (LC_{50}) og dermed er værdien under afskæringsværdien på 10 mg/l anvendt i NanoRiskCat.

Det er vigtigt at understrege, at NanoRiskCat ikke skal ses som en mærkningsordning, men at NanoRiskCat alene skal bruges til at udføre en evaluering af et nanomateriale under de fysiske forhold hvori det forekommer i produktet. NanoRiskCat vurderer således ikke eksponering og effekter fra de øvrige ingredienser, bestanddele og urenheder i produktet, og der tages heller ikke hensyn til den konkrete indholdsmængde eller koncentration af nanomaterialet i produktet. Således er NanoRiskCat rettet mod brugen af generiske anvendelsesbeskrivelser og scenarier som for eksempel er beskrevet i de processer, produktkategorier, osv., der anvendes i REACH vejledningen. En NanoRiskCat farvekode er således anvendelsesspecifik, og en farvekode for én anvendelse kan dermed ikke overføres til en anden. Ligeledes vil NanoRiskCat farvekoder i sig selv ikke kunne bruges til generelle vurderinger sikkerheden af nanomaterialer som et hele. En væsentlig styrke ved NanoRiskCat er, at det kan bruges, selv i tilfælde, hvor manglen på data er fremtrædende og hæmmer gennemførelsen af traditionelle risikovurderingsprocedurer. En anden styrke er, at NanoRiskCat hjælper brugerne med at sortere i den litteratur, der med stigende hastighed bliver publiceret indenfor nano(øko)toksikologi. En tredje fordel ved NanoRiskCat er at resultaterne let kan kommunikeres med andre interesserede parter.

En væsentlig svaghed ved NanoRiskCat er, at mange af de afskæringsværdier, der anvendes primært i de miljømæssige farevurderinger er baseret på en masse-afhængig dosis (altså f.eks. mg/l), vel vidende om at der løbende foregår en diskussion af hvilket dosis-mål, der bedst kan bruges til effekt-beskrivelse i nano(øko)toksikologi. Derudover er den proces, hvorved farvekoden er tildelt i forbindelse med sundhedsfarevurderingen af nanoformen af et bestemt materiale primært baseret på videnskabelige ekspertvurderinger og en mere sammenfattende vurdering af evidensen for mutagenicitet, carcinogenicitet, respiratorisk toksicitet, osv. Da ekspertvurderinger af den selvsamme datagrundlag kan variere, kan såvel konklusionen som den deraf følgende farvekodningen ligeledes variere fra bruger til bruger. Det er imidlertid ikke muligt at give klare retningslinjer på dette tidspunkt for, hvordan man gennemfører en mere holistisk vurdering af de menneskelige og miljømæssige fare forbundet med nanoformen af et bestemt materiale. ***Det helt afgørende i den forbindelse er at brugerne af NRC forklarer hvilket litteratur de har identificeret som relevant og argumenterer for hvordan de fortolker de reporterede resultater og tildeler diverse farvekoder.***

Selvom NanoRiskCat er designet til at hjælpe brugere med at identificere, kategorisere, rangordne og kommunikere den nuværende viden om de nanomaterialer som de anvender, er det vigtigt at understrege at NRC i sig selv ikke fører direkte til en beslutning. Derimod giver NRC et mere kvalificeret grundlag for at tage en beslutning ved at medtage en række indikatorer som samlet set afgør om eksponering er sandsynlige (eller usandsynlig) og om nanomaterialet kan have problematiske, skadelige egenskaber.

De beslutninger, der kan efterfølge brugen af NanoRiskCat vil være interessent-afhængige. Regulerende myndigheder kunne fx bruge NRC til på screeningsbasis at udpege anvendelser, hvor risikohåndteringsmæssige foranstaltninger kan overvejes nøjere, fx udarbejdelse af retningslinjer for kontrollerede anvendelser eller evt. at undersøge mulighederne for at indføre forbud eller anvendelsesbegrænsninger eller pege på hvor der savnes viden. Virksomheder kan bruge NanoRiskCat til at kommunikere, hvad de ved om virkningerne af de nanomaterialer, de bruger, hvorefter de ligeledes kan vurdere behovet for at udvikle retningslinjer for sikker brug. Det kunne fx. være ved at ændre på formuleringen eller anvendelsen af produktet eller ved at designe mere sikre nanomaterialer. Ligeledes er det en mulighed at udarbejde retningslinjer til professionelle slutbrugere og forbrugere om sikker anvendelse af nanomaterialer. Hvis virksomheder eller andre gør deres NRC profiler offentligt tilgængelig kan forbrugere endvidere bruge NanoRiskCat til at foretage en foreløbig vurdering af en række nano-baserede produkter. Endelig, kan NRC bruges til at øge vidensdelingen om eksponeringen og effekten nanomaterialer og NanoRiskCat kan bidrage til en uafhængig vurdering og indgå i en informeret dialog om nanorisiko mellem forskere, forbrugere, virksomheder og myndigheder.

Eftersom beslutninger, der kan følge af brugen af NanoRiskCat er interessent-afhængige, er det vigtigt at understrege, at farvekoderne opnået i NanoRiskCat ikke bør ses som en absolut kategorisering. Det bør snarere fungere som et skridt i en iterativ proces, hvor interessenterne i risiko-relaterede spørgsmål kan nå frem til en fælles forståelse af potentialet for eksponering og effekter af nanomaterialer i bestemte produkter. Det er vigtigt at understrege, at det ikke har været muligt inden for rammerne af dette projekt at foretage en yderligere validering af NRC konceptet. For at opnå et mere færdigt værktøj, anses det derfor for nødvendigt at foretage yderligere validering af konceptet, herunder udføre flere forskellige casestudier, og herigennem eventuelt tilpasse processerne og de kriterier der benyttes i NRC for at opnå et screeningsværktøj, der er så bredt anvendeligt, praktisk og informativt som muligt.

Executive Summary

Nanomaterials are being used in a rapidly increasing number of products available for industries and private consumers. The number of nanomaterials that can be manufactured using nanotechnologies is immense and the improved material properties enable use in multiple different products. During the last decade more and more evidence has emerged in the scientific literature suggesting that some nanomaterials may have hazardous properties.

With this background, the Danish Environmental Protection Agency has identified a need for developing a new concept that can provide support to companies and regulators in regard to assessing, ranking and communicating what they know about the risks of nanomaterials in specific product uses. In this case, risk should be defined as a combination of the likelihood of exposure and adverse effects, i.e. any chance of an adverse outcome to human health, the quality of life, or the quality of environment.

Through this project, DTU Environment and the National Research Centre for the Working Environment have initiated the development of a screening tool, NanoRiskCat (NRC), that is able to identify, categorize and rank exposures and effects of nanomaterials used in consumer products based on data available in the peer-reviewed scientific literature and other regulatory relevant sources of information and data. The primary focus was on nanomaterials relevant for professional end-users and consumers as, as well as nanomaterials released into the environment.

The wider goal of NanoRiskCat is to help manufacturers, down-stream end-users, regulators and other stakeholders to evaluate, rank and communicate the potential for exposure and effects through a tiered approach in which the specific applications of a given nanomaterial are evaluated. This is done by providing detailed guidance on mapping and reporting of the:

1. Exposure potential for professional end-users
2. Exposure potential for consumers
3. Exposure potential for the environment
4. A preliminary hazard evaluation for humans
5. A preliminary hazard evaluation for the environment

A generic template for mapping and reporting these five aspects for a specific application of a given nanomaterial has been developed and can be found in Appendix 1 of this report.

In its simplest form, the final outcome of using NanoRiskCat for a nanomaterial in a given application will be communicated in the form of a short title describing the use of the nanomaterial (e.g. MeO in ship paint) and a five-color coded dots (e.g.,), where the first three dots always refer to potential exposure of professional end-users, consumers and the environment in that

sequence and the last two colors always refer to the hazard potential for humans and the environment. The colors signify whether the indications of exposures or effects separately are high (red), medium (yellow), low (green), or unknown (grey).

The color-coding of the dots representing the exposure potential (dost numbers one to three) is based on the generic use descriptor system established by the European Chemicals Agency (ECHA) in the current REACH Guidance on information requirements and chemical safety assessment Appendix R.124. For each use category, a color code (●, ●, ● or ●) has been assigned based on 1) the location of the nanomaterial (bulk, on the surface, liquid or airborne) and 2) a judgment of the potential for nanomaterial exposure based on the description and explanation of each process, product category, technical function, article and environmental release category provided in the REACH Guidance.

When assigning a color to the dot representing potential human health hazards (dot number four) related to the specific application of a given nanomaterial the following indicators/qualifiers should be considered:

1. Does the ***nanomaterial*** fulfil the HARN[5] paradigm?

2. Is the ***bulk form*** of the nanomaterial known to cause or may cause serious damaging effects, i.e. is the bulk form classified according to the CLP[6] with regard to one or more serious health hazards such as germ cell mutagenicity, carcinogenicity or reproductive toxicity in category 1A, 1B or 2?

3. Is the ***bulk form*** of the nanomaterial classified for other less severe adverse effects according to the CLP such as skin corrosion/irritation category 2 and specific target organ toxicity-single exposure category 3?

4. Is the specific ***nanomaterial*** known to be acute toxic?

5. Are there indications that the ***nanomaterial*** causes genotoxic, mutagenic, carcinogenic, respiratory, cardiovascular, neurotoxic or reproductive effects in humans and/or laboratory animals or has organ-specific accumulation been documented?

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[4] ECHA 2010 Guidance on information requirements and chemical safety assessment Chapter R.12: Use descriptor system Version 2. Available: http://guidance.echa.europa.eu/docs/guidance_document/information_requirements_r12_en.pdf (Accessed 25-04-2011)

[5] HARN refers to High Aspect Ratio Nanoparticles indicating that the nanoparticles have a length to diameter aspect ratio greater than 10 to 1. Furthermore, it is required that: 1) The diameter of the fibres must be thin enough pass ciliated airways; 2) the length must be long enough to initiate the onset of e.g. frustrated phagocytosis and other inflammatory pathways; and 3) the nanomaterials must be biopersistent (Tran ***et al.*** 2008).

[6] Regulation (EC) No 1272/2008 of the European Parliament and of the Council of 16 December 2008 on classification, labelling and packaging of substances and mixtures, amending and repealing Directives 67/548/EEC and 1999/45/EC, and amending Regulation (EC) No 1907/2006

The human hazards information on the bulk form of the material may be used as a starting point in order to describe a possible minimum level of concern in regard to the toxicological profile for the nanomaterial. A guiding principle is that information about the bulk form of the material can be used under the assumption that any toxicological and ecotoxicological effects of the nanomaterial are equal to or larger than those reported on for the bulk material. Thus hazard data on the bulk material forms the basis of the lowest level of concern with regard to the nanomaterial.

In NRC, indications of the level of environmental effects (dot number five) should include considerations of whether the ***nanomaterial*** in question is reported to be:

1. Hazardous to environmental species?
2. Persistent?
3. Bioaccumulative?
4. Leading to potentially irreversible harm to the environment (e.g. ecosystem effects)?
5. Readily dispersed?
6. Novel?

It is important to note that NanoRiskCat is a stepwise and tiered approach in the sense that once a color code has been triggered this finalizes the screening process.

To help communicate the scientific reasoning behind the human health and environmental hazard categorization and the assigned color code, a number of standard sentences have been included in the framework. These sentences are primarily meant to reflect whether the categorization has been reached based on ***in vivo*** or ***in vitro*** studies and in regard to which effect or endpoint. Depending to the final categorization in regard to human health and environment, the user of NRC has to select one or more of those sentences that best reflect the scientific basis for assigning the color code.

In order to illustrate the feasibility of NanoRiskCat two nanomaterials (titanium dioxide and C_{60}) were used as training sets in two different applications i.e. C_{60} used in a lubricant and TiO_2 used in sunscreen. These examples were chosen order to be used in the development of the concept but they are also included in the current report in order to illustrate the applicability of NanoRiskCat. The NanoRiskCat code of C_{60} used in a lubricant was ●●●|●● as the exposure potential is high for professional end-users, comsumers and the environment. The human hazard potential was evaluated to be medium (yellow) based on ***in vitro*** evidence indicating at least one human hazard specifically associated with C60, whereas the environmental hazard potential was evaluated to be high (red) because studies indicate that C60 may cause lethal or sublethal effects on fish and crustaceans on levels below the cut-off values set in NanoRiskCat (i.e., LC_{50} or EC_{50} values < 10 mg/l). For TiO_2 in sunscreen the NanoRiskCat code was ●●●|●● as the exposure potential is high (red) for professional end-users, comsumers and the environment. The human and environmental hazard potential was also evaluated to be high

(red) based on ***in vivo*** data of severe effects of nano-TiO_2. The potential of environmental effects was also evaluated as high on basis of one study with daphnids where LC_{50} was 2 mg/L which is under the cut-off value of the NRC concept.

It is important to underline that NanoRiskCat is not a product label and NanoRiskCat is only to be used for evaluating the nanomaterial as an ingredient under the physical conditions it occurs in the product. NanoRiskCat does not evaluate exposure and effects from the other constituents and impurities in the product nor does it take into account the specific content of nanomaterial in the product. Thus, NanoRiskCat is directed towards the generic use descriptors and scenarios, which for instance are apparent in the product categories used in REACH. Although NanoRiskCat is generic in nature and can be used on all kinds of nanomaterials and applications, the NanoRiskCat color code itself is application-specific. Thus, a NanoRiskCat color code does not in itself allow for an overall evaluation of risks associated with a given nanomaterial.

A significant strength of NanoRiskCat is that it can be used even in cases where lack of data is prominent and hampers the completion of traditional risk assessment procedures. Another is that the results of NanoRiskCat can be easily communicated to interested parties. A significant weakness of NanoRiskCat is that many of the cut-off values used primarily in the environmental hazard evaluation is based on dose-by-mass which we know is probably not valid for all nanomaterials as it is an ongoing discussion on which dose-metrics will be the best to use in nano-ecotoxicology. Furthermore, the process by which the color code is assigned to human hazards associated with the nanoform of a given material is based primarily on scientific expert judgement and a holistic assessment of the evidence of mutagenicity, carcinogenicity, respiratory toxicity, etc. As expert interpretation of scientific literature vary, so can the conclusion reached and the human hazard color code assigned to nanomaterial. It is not possible to provide clear-cut guidance and rules at this point in time for how to complete holistic evaluation of the human and environmental hazards associated with the nanoform of a given material. ***It is crucial in this context that the users of the NRC explain what literature they have identified as relevant and explain how they interpret the reported results and assign the various color codes in the NRC template provided in Appendix 1.***

The result of NRC does not lead directly to an decision in contrast to other decision-making tools available for nanomaterials, but NRC does provide a informed and structured foundation for decision-making by including a number of indicators that define whether exposure and effects are likely (or unlikely) to occur and whether the nanomaterial may have harmful properties of concern.

Decisions that could come out of using NanoRiskCat are stakeholder-dependent. Regulators could use NRC as a screening tool to identify possible uses where risk management measures may be further examined e.g. to develop guidance on controlled uses, or to evaluate whether specific restrictions would be required or to indentify data needs. Companies can use NanoRiskCat to communicate what they know about the exposures and effects of the nanomaterial they use, assess the need to develop guidance for safe uses that e.g. limit exposures by changing the product formulation or the use of the

nanoproduct or work systematically with designing safer nanomaterials. Likewise, the company could develop guidelines for professional end-users and consumers about the safe uses of their nanomaterials and products. Down-stream users (e.g. consumers) can use NanoRiskCat to make a preliminary assessment of a range of nanomaterials as a mean to select the seemingly safest material. Finally, independent parties such as academics and non-governmental organizations can use the tools to learn more about what companies know about exposures and effects of their nanomaterials and they can use NanoRiskCat to do their own independent evaluation and subsequently engage in an informed dialogue about nanorisks with companies and regulators. It is finally important to stress that the color coding obtained in NanoRiskCat should not be seen as an absolute categorization. It rather serves as a step in an iterative process in which stakeholders in risk-related issues can reach a common – and guided - understanding of the level of potential exposures and effects of nanomaterials in specific products.

As decisions that could come out of using NanoRiskCat are stakeholder-dependent, it is important to emphasize that it has not been possible within the framework of this project to validate the NRC concept further. To promote a wider use of the tool it is considered necessary to perform additional case studies and if relevant adjust the processes and decision criteria in order to obtain a screening tool as informative and practical as possible.

1. Background and aim

Nanotechnology is an emerging technology that it is developing with rapid speed in multiple directions and in many scientific fields and industrial sectors. The term "nanotechnology" covers several methods and technologies. Some of the most well-known technologies and methods include chemical vapour deposition, atomic force microscopy and scanning probe- and tunnelling microscopy, but the number of methods, processes and techniques easily exceeds 30 (BSI 2007 a, b).

The number of nanomaterials that can be manufactured using nanotechnologies are immense including, for instance, C_{60}, carbon nanotubes, micelles, self assemble monolayers, dendrimers, and aerogels in all kinds of size and shapes. Hence the nature of nanomaterials differs even more than the techniques. In this work, we adhere to the ISO definition of a nanomaterial which defines a nanomaterial as a ***"material with any external dimension in the nanoscale or having internal structure or surface structure in the nanoscale"*** where the nanoscale again is defined as the "size range from approximately 1 nm to 100 nm" (ISO 2008).

Nanomaterials are being used in a rapidly increasing number of products available for industries and private consumers, but during the last decade more and more evidence has emerged in the scientific literature that some nanomaterials might have hazardous properties (for a comprehensive review, see Stone ***et al.*** 2009). This lead the Danish Environmental Protection Agency to identify a need for developing a new concept that can provide support to companies and regulators in regard to assessing, ranking and communicating the risks of nanomaterials in specific uses in products.

The aim of this project is therefore to develop a conceptual framework for a screening tool, NanoRiskCat, for risk evaluation, categorization and ranking of nanomaterials based on data available in the peer-reviewed scientific literature and other regulatory relevant sources of information and data. The primary focus will be on nanomaterials relevant for professional end-users, consumers as well as released to the environment. Professional end-users are defined as entities that use products containing nanomaterials professionally and are not to be understood as workers that produce the products.

There are many data gaps and unknowns in relation to specific knowledge about exposure, hazards and risks related to the use of nanomaterials. However, it is important to stress that the screening tool proposed here is intended to be used on the basis of existing experience regarding, for example, general knowledge about the exposure potential in different product types and use categories. For evaluation of potential hazards read-across from information on the bulk material will be used if appropriate in order to describe the most probable toxicological profile of the nanoform of the material. Thus hazard data on the bulk material is be used to form the basis of the minimum level of concern with regard to the nanomaterial.

The aim of this project has been to develop an easily comprehensible ap-

proach that - when fully developed and validated - can help manufacturers, down-stream end users, regulators and other stakeholders in making decisions in situations where the safety of nanomaterials are being questioned.

Before going into detail with NanoRiskCat a systematic evaluation of existing ranking and assessment concept and frameworks for chemicals and nanomaterials will be performed (Chapter 2) in order to get inspiration from these. This is followed by a description of the overall structure of NanoRiskCat (Chapter 3) as well as the evaluation criteria used to assess the exposure potential of a given nanomaterial application and to evaluate the hazard profile of a specific nanomaterial. This includes two illustrative examples of using NanoRiskCat on specific nanomaterial used in consumer products or industry (Chapters 4) and a discussion about the potential use(s) and pros and cons of NanoRiskCat (Chapter 5).

2. Existing ranking and assessment concepts for nanomaterials

Traditional risk assessment of chemicals consists of hazard identification, dose-response assessment, exposure assessment and risk characterization. Applying traditional risk assessment to nanomaterials holds a number of challenges that have yet to be overcome. Traditional risk assessment is based on the principle that the "dose [by mass] makes the poison" (Baun and Hansen 2008), but scientific evidence indicate that this might not be the case with nanomaterials (Stone ***et al.*** 2009) and that other materials properties such as size, surface area, surface chemistry, and reactivity need to be considered as well (Hansen et al 2007). Traditional risk assessment furthermore assumes that a "safe level of exposure" can be established and that human and environmental exposure can be assessed or estimated. There is disagreement about whether these assumptions are valid when it comes to nanomaterials due to lack of consensus on the appropriate hazard metric and index and report of nanomaterial exposure. According to Paik ***et al.*** (2008) and Hansen (2009) there are numerous barriers that need to be overcome before traditional risk assessment can be applied to nanomaterials and according to Hansen (2009) this might take 20-25 years. The question then becomes what to do in the meanwhile and how to report on what is known about a given nanomaterial and its uses?

A number of concepts, approaches and frameworks currently exist that intend to estimate and control to risks of nanomaterials. Examples of these includes the American "Control Banding Nanotool" developed to assess and control the risks of nanomaterials when working in the laboratory (Paik ***et al.*** 2008, Zaik ***et al.*** 2009), and the more holistic "Swiss precautionary matrix" developed by Höck ***et al.*** (2008). A number of concepts and tools also exist which were originally develop for the safe handling of chemicals such "Comprehensive Environmental Assessment" (Davis 2007) and "MultiCriteria Decision Analysis" (Linkov ***et al.*** 2007, Tervonen ***et al.*** 2009) and these might also be relevant to explore in regard to nanomaterials.

In this chapter the content of these frameworks and tools will be briefly described and finally identified pros and cons of these tool will be discussed and listed in a table for comparison. The purpose of doing this is to give an overview of existing frameworks in order to assure that the development of NanoRiskCat is developed under the consideration of the knowledge gained from the already developed frameworks. Furthermore, some of the approaches used in existing frameworks have served as a source of inspiration for the development of NanoRiskCat and this should be acknowledged.

2.1 British Standards (2007)

In 2007 British Standards published one of the first reports with actual suggestion on how to assess the hazard of handling of particulate nanomaterials in the work environment. The proposed framework is fairly simple as the purpose was to develop a set of practical guidelines.

The approach proposed follows the framework outlined in the British Control of Substances Hazardous to Health Regulations (COSHH) 2002 which comprises of eight main steps:

1. identify the hazards and assess the risks.
2. decide what precautions are needed.
3. prevent or adequately control exposure.
4. ensure that control measures are used and maintained.
5. monitor the exposure.
6. carry out appropriate health surveillance.
7. prepare plans and procedures to deal with accidents, incidents and emergencies.
8. ensure employees are properly informed, trained and supervised.

In the proposed framework the availability of information is linked to assumptions about hazards and the need for exposure controls in the sense that if little is known about the material, it will be necessary to treat it as highly hazardous and apply tighter exposure controls.

When considering the available hazard information the BSI (2007) suggests starting with categorizing nanomaterial-associated hazards into four groups:

1. Fibrous a high aspect ratio insoluble nanomaterial.
2. Any nanomaterial which is already classified in its larger particle form as carcinogenetic, mutagenic, asthmagenic or a reproductive toxicant (CMAR).
3. Insoluble or poorly soluble nanomaterials not in the fibrous or CMAR category.
4. Soluble nanomaterials not in fibrous or CMAR category.

According to the BSI (2007) it should be assumed by default that all categories of nanomaterials have a hazardous potential, which is greater than that of the larger, non-nanoscale forms of the material.

For exposure assessment, qualitative assessment of the exposure level or quantitative measurements of air concentrations with “appropriate” measuring instruments. One parameter in the exposure scenario is reserved to methods to reduce exposure whereas the rest of parameters describe the actual use phase under which is there is an exposure risk and who many might be exposed.

The calculation method to be used for estimating of the exposure risks is not described, however the BSI (2007) notes that the chosen parameters

could be insufficient given the lack of knowledge regarding nanoparticles. BSI state that an exposure assessment should ideally be based on measurements with ”appropriate” apparatus and that relevant measurements should be included in the assessment as much as possible. Given current knowledge about nanoparticles, it is likely that much of the information asked for will be considered insufficient according to BSI (2007). Hence focus of the evaluation process should be on identification of those use scenarios for which a high exposure is likely and/or highly uncertain followed by a more detailed analysis of these uses. BSI (2007) underline the necessity to err on the side of caution and to determine where significant doubt exists and develop a prioritized plan to collect additional information about exposure levels.

Based on the hazard evaluation and the exposure assessment, the BSI (2007) suggest handling of the risk following a hieratical prioritization. Priorities are decided on the basis of assessments of:

- the most serious risks to health
- the risks that are likely to occur soonest
- the risks that can be dealt with soonest

2.2. Control Banding Nanotool

In 2008 Paik ***et al.*** (2008) presented their Control Banding Nanotool which is based on the paradigm established by COSHH Essentials (HSE, 2005) as well and apply only to work environment. The backbone of Control Banding Nanotool is the concept of ‘bands’ to assist in preventing exposure to chemicals. The control band to be implemented for a given operation is based on the overall risk level (RL) determined for that operation which again is determined by a ‘severity’ score and a ‘probability’ score.

The overall severity of the nanoscale materials should be evaluated considering a number of factors such as surface chemistry, particle shape, particle diameter, solubility, carcinogenicity, and reproductive, mutagenicity, dermal toxicity of the nanomaterial itself as well as the Occupational Exposure Level, the carcinogenicity and the reproductive and dermal toxicity of the parent material. Based on available information in the literature, a severity score is given to each factors e.g. in regard to shape the highest severity score of 10 points is given to fibrous or tubular shaped. Particles with irregular shapes (other than tubular or fibrous) are given a medium severity score of 5 points and ‘compact or spherical’ nanoparticles results in 0 pts. Similarly, ‘1–10 nm’ particle diameter results in 10 points, ‘11–40 nm’ results in 5 points,41–100 nm’ results in 0 points and a rating of ‘unknown’ results in 7.5 points. 0 points were assigned as an indication of low ‘relative’ severity and does not indicate that no effect has been observed. If the information for a given factor is ‘unknown’, 75% of the point value of ‘high’ would be given for that factor.

The overall severity score is determined based on the sum of all the points from the severity factors and the maximum score is 100. An overall severity score of 0–25 was considered low severity, an overall severity score of 26–50 was considered medium severity, an overall severity score of 51–75

was considered high severity and an overall severity score of 76–100 was considered very high severity.

A combination of severity and probability leads to an overall risk level (RL) ranging from 1 to 4 for which specific control strategies are prescribed i.e. RL1= General ventilation, RL2= fume hoods or local exhaust ventilation, RL3= containment and RL4= seek professional advice.

For a hypothetical nanotechnology operation for which nothing was known (other than it involves nanoparticles), the required control would be 'containment' (RL3). In this scenario, if just one rating for any of the factors was later determined to be high, with all other ratings remaining as unknown, the tool would assign this activity as 'seek specialist advice' (RL4) and require the maximum control.

2.3. The Swiss Precautionary Matrix

The Swiss Precautionary Matrix developed of Höck ***et al.*** in 2008 and revised in 2010 (Höck ***et al.*** 2010) was published almost at the same time as the Control Banding Nanotool, but the Swiss Precautionary Matrix also addresses risks to consumers and environment. The stated purpose of the Swiss Precautionary Matrix is to develop a system that enables users (i.e. businesses) to estimate the "nanospecific precautionary need" of synthetic nanomaterials and their applications for employees, consumers and the environment, based on a number of selected parameters. The need for precaution is estimated for a normal use and worst-case (WC) scenario and is seen as a function of the:

1. Potential effect (W)
2. Potential human exposure / potential input into the environment (E)
3. Nano-relevance (N)
4. Specific framework conditions: Information about the life cycle (S)

It is assumed that nanospecific risks arise only if there is a possibility of two-dimensional (nanorods) or three-dimensional (nanoparticles) nanoscale particles or their agglomerates being released. Nanoscale is recommended to be extended to 500 nm (Höck ***et al.*** 2010).

The Precautionary Matrix is made up of modules of various input parameters that have to be scored by the user from 1 to 9 (low = 1, medium 5, high = 9 or hours =1, days-week=5, months=9) for the purpose of calculating the precautionary need. A template for the precautionary matrix is available as a hard copy and as a computerized version available at:
http://www.bag.admin.ch/themen/chemikalien/00228/00510/index.html?lang=de

When filling out the matrix, users are advised to carry out their own investigations on human exposure, inputs into the environment and the effects of nanomaterials as well as draw on data from the literature and experts, if applicable. If the requested information is not available, the value that

would ultimately give the highest precautionary need must be used (Höck ***et al.*** 2010).

Assigning scores to the various input parameters is of key importance and the guideline for how to apply the Swiss Precautionary Matrix offer various guidance on how to derive scores. For instance, the potential effect of nanoparticle and nanorods on health and the environment is estimated by:

1. Redox activity and/or catalytic activity of the nanoparticles and rods present in the nanomaterial.
2. Stability of the nanoparticles and rods present in the nanomaterial under the relevant conditions in the body or the environment.

As there are currently no internationally approved methods for determining the nanospecific redox activity or catalytic activity of nanoparticles and rods, an approximate evaluation can be achieved with the following the listing of comparative nanoparticles and rods set forward by Höck ***et al.*** (2010).

Stability is evaluated in regard to half-life of the nanoparticles and rods present in the nanomaterial in the body or under environmental conditions taking into account the resistance of the nanoparticles and rods used to dissolution, chemical or physical change, sintering or particle degradation.

The exposure part of the Swiss Precautionary Matrix is rather simple and based on estimation of the actual (worst-case) airborne exposure or exposure over the course of 24 hours or a workday, if talking about workers.

The exposure level is estimated from the type of exposure, the measured or estimated exposure and frequency. In regard to type of exposure, one can chose between nanomaterials in the form of airborne dust, suspended in liquids, and more or less stable matrixes. The first two type of exposure both lead to a full inhalation risk, whereas the later two gives a relative inhalation risk of free nanomaterials ranging from 0.0001-10 %. This, however this is highly uncertain and depends heavily on the material and the activity. The score given in regard to the type of exposure (e.g. 1 for airborne dust of nanomaterials) is multiplied with the score given to the level of daily exposure (<25μg = 1 point), <250 μg = 5 point; >250 μg = 9 point) and frequency of exposure (daily = 9 point, weekly= 5 point or monthly = 1 point). The limits for exposure are increase by a factor 10 in regard to estimation of exposure during an accident.

Once all the input parameters have been scored, the precautionary need can be calculated by multiplying the potential effect (W) with the potential human exposure/input into the environment (E). Then Specific framework conditions: Information about the life cycle (S) is added and the sum is multiplied by the Nano-relevance (N):

$$V = N * (W * E + S)$$

Based on the total score of the precautionary need (V) a general classification can then be made of various use of nanomaterials into a Class A and a Class B (see table 1).

Table 1: Classification of nanomaterials based on overall score in the Swiss Precautionary Matrix (Höck *et al.* 2010)

Score	Classification	Importance
0-20	A	The nanospecific need for action can be rated as low even without further clarification
>20	B	Nanospecific action is need. Existing measures should be reviewed, further clarification undertaken and, if necessary measures to reduce the risk associated with manufacturing, use and disposal should be implemented

Höck ***et al.*** (2010) does not offer a model for risk handling, but a closer look into whether there is a real nanospecific risk is recommended if the score exceeds 20 point. Hence, a weekly handling of nanomaterials with a intermediary daily airborne exposure of 25 - 250 µg would require a closer evaluation of the nanospecific risk, but not a monthly handling which gives more than 250 µg.

As a general rule, a precautionary matrix applies to just one specific type of nanoparticles and rods in a precisely defined environment. If the physical environment (e.g. solvent, matrix/substrate, state of aggregation, etc.) or the conditions of use change, a new precautionary matrix has to be completed for this situation. A new matrix also has to be completed if the original nanoparticles and rods are changed into defined new nanoparticles and rods during use, for instance through rapid dissolution of a coating.

The precautionary matrix can however be used to estimate the precautionary need for the health of employees and consumers and for the environment throughout a nanomaterial's entire life cycle. A separate precautionary matrix must be created for each process under review.

2.4 Genaidy *et al.* (2009)

Genaidy ***et al.*** (2009) represent an example of a qualitative risk assessment method which has successfully been applied in a company producing Carbon Nanofiber (CNF). In contrast to the other methods presented here, Genaidy ***et al.*** (2009) also considers the application of other chemical and other phases ranging from production to storage of bags.

The approach suggested by Genaidy ***et al.*** (2009) consists of a phase 1 focused on generation of improvement actions and a phase 2 focused on transformation of improvement actions into health education awareness and combined health protection/promotion interventions.

The first phase consists of three steps. In the first step the 'probability' of exposure and the 'severity' of consequences of workers' exposure to physical and non-physical related hazards is assessed using a hazard analysis instrument termed a "HAI". Each hazard is evaluated in terms of:

1. probability of exposure using one of five descriptors, i.e. "Frequent", "Probable", "Occasional", "Remote", and "Improbable"; and
2. severity of consequence in terms of four levels, i.e. "Catastrophic", "Critical", "Marginal", and "Negligible".

The second step of phase 1 involves the transformation of hazard measurement into a risk code as follows:

1. The probability of exposure and severity of consequences for a given hazard or work environment characteristic are entered into a risk map derived by Genaidy ***et al.*** (2009) on the basis of knowledge extracted from a number of consensus meeting with risk assessment experts;
2. A risk code is determined depending on the probability–severity values. There are five risk levels (Abdallah ***et al.***, 2004):
3. "Very high" or "red" — substantial changes should be planned immediately followed by incremental changes;
4. "High" or "orange" — substantial changes should be planned in the short term, followed by incremental changes;
5. "Moderate" or "yellow" — one should start with incremental changes then explore substantial changes if needed;
6. "Low" or "blue" — one should explore incremental changes;
7. "Very low" or green" — sustain the current situation.

During the third step of phase 1 the Risk scores are classified into two-tier classification:

1. Risk score b3 (i.e., "very high", "high", and "moderate"), and
2. Risk score N3 ("low and very low")

The two-tier classification along with the priority scores of improvement actions from step 1 is used to identify:

1. short-term improvement actions — high-priority (step 3a) and medium-priority (step 3b); and,
2. long-term improvement actions step 3c.

The former address the "red" and "orange" priority levels of hazards and the methodology applied focuses on reducing the red and orange scores into blue in the short term with no lesser value than "3" or yellow. Step 3b address the yellow scores into blue in the short term whereas step 3c calls for continuous improvement to change blue characteristics into "green", if possible (Genaidy ***et al.*** 2009).

In contrast to the other methods and approaches presented here, the approach suggested by Genaidy ***et al.*** (2009) offers a prescribed approach for handling of identified risks during phase 2. Improvement actions are however not automatically prescribed as in the case on the approaches using

Control Banding concepts. Instead, improvement actions is expanded on by adding the type of intervention (e.g. health protection/promotion/education awareness) and the criteria required for their implementation and the proposed approach makes use of the strategies researched by Haddon (1973, 1980) for the reduction of risks arising from hazards of all kinds. The strategies include: (1) elimination of hazard creation; (2) reduction of the amount of hazard brought into being; (3) prevention of hazard release; (4) modification of distribution rate and spatial of hazard release from its source; (5) hazard separation via time or space; (6) hazard separation by interposition of a material barrier; (7) modification of relevant basic qualities of hazard; (8) rendering the target to be protected more resistant to damage from that hazard; (9) counter damage already done by environmental hazard; and, (10) to stabilize, repair and rehabilitate the damaged object.

For each of the intervention strategies four criteria were applied: applicability, benefit, cost and feasibility. If one of Haddon's strategies is considered applicable the other criteria are considered. For the evaluation of benefits and cost, Genaidy ***et al.*** (2007) suggest that preference is given to any high benefit/low cost strategy (Option I) followed by any high benefit/high cost (Option II) and low benefit/low cost (Option III) strategy and finally low any benefit/ high cost (Option IV) strategy. Feasibility is used as a final criterion and should be accessed in the short-term (yes) as well as in the long-term (no).

2.5 MultiCriteria Decision Analysis and risk-based classification system for nanomaterials

A number of multiple criteria decision analysis (MCDA) methods exist and a common purpose of these methods is to evaluate and choose among different decision alternatives based on multiple criteria using systematic, structured and transparent analysis in contrast to ''ad hoc'' decisions (Linkov ***et al.*** 2006, Hansen 2010). MCDA methods vary in regard to various optimization algorithms deployed, in the types of value information needed and in the extent to which they are dependent on computer software. Some MCDAs techniques rank options against each other whereas others identify a single optimal alternative and again others differentiate between acceptable and unacceptable alternatives (Linkov ***et al.*** 2007). Linkov ***et al.*** (2007) have illustrated the theoretical applicability of MCDA to evaluate three hypothetical nanomaterials whereas Tervonen ***et al.*** (2009) have used an outranking model termed Stochastic multicriteria acceptability analysis (SMAA-TRI) to group nanomaterials (e.g., C_{60}, MWCNT, CdSe) in various risk classes (extreme, high, medium, low, and very low risk) for screening level risk assessments. More specifically, Tervonen ***et al.*** (2009) set forward a number of criteria, both in terms of nanoparticle properties as well bioavailability, bioaccumulation and toxic potential. Quantitative criterion were either measured or based on expert judgments whereas qualitative criteria were established in terms of ordinal classes: 1 was the most favourable (least risk) value class, while 5 the least favourable (highest risk). Weight bonds were assigned to the various criteria by the authors e.g. toxic

potential 0.3–0.5, bioavailability and bioaccumulation potentials 0.02-0.08 and the rest of the criteria were assigned weight bounds of 0.05–0.15. A cutting level within the range of 0.65–0.85 was then used to define the minimum sum of weights for the criteria that must be in concordance with the outranking relation to hold.

2.6 Environmental Defense & DuPont Nanorisk framework

An example of a framework that has already been used by industry is the Nano Risk Framework which was jointly released in early 2007 by Environmental Defense and the DuPont Corporation (Environmental Defense and DuPont 2007). This framework describes a process for "ensuring the responsible development of nanoscale materials." (Environmental Defense and DuPont 2007). The framework can be used freely by companies and other organizations. The intent of the framework "is to define a systematic process for identifying, managing, and reducing the potential environmental, health, and safety risks of engineered nanomaterials across all stages of a product's 'lifecycle'." It is meant to offer a voluntary approach to facilitate the responsible development of nanomaterials by companies, as well as private and public research institutions. The framework is designed to be used iteratively at different stages of development advancement including basic R&D, prototyping, pilot testing, test marketing, and finally full-scale commercial launch as well as when new information becomes available.

The framework consists of six distinct steps:

1. Develop a general description of the nanomaterial and its intended uses, based on information already available, and identify analogous materials and applications that may help fill data gaps in this and other steps.
2. Develop profiles of the nanomaterial's properties, inherent hazards, and associated exposures, considering all the elements of the nanomaterial's full lifecycle and also considering that a material's properties, hazards, and exposures may change during.
3. Evaluate all of the information generated in the profiles and identify and characterize the nature, magnitude, and probability of risks of the nanomaterial and its application. Gaps in the lifecycle profiles should be prioritized and a decision should be made on how to address them.
4. Evaluate the available risk management options and recommend a course of action, including engineering controls, protective equipment, risk communication, and product or process modifications.
5. Decide alongside key stakeholders, experts, and decision-makers whether or not, or in what capacity, to continue development and production and document these decisions as well as their rationale, and share appropriate information with relevant stakeholders.
6. Update and re-execute the risk evaluation regularly or as necessary to ensure that risk management systems are working as expected and adapt in the face of new information or conditions.

The authors clarify that, ***"[t]hrough these six steps, the framework seeks to guide a process for risk evaluation and management that is practical, comprehensive, transparent, and flexible."*** (Environmental Defense and DuPont 2007). The ED and DuPont framework is further intended to guide users through information generation and help them update assumptions, decisions, and practices as new information becomes available. At various stages in the product-development process, the document provides a worksheet to help participants: 1) organize, document, and communicate the information they have about their material; 2) acknowledge that information is incomplete; 3) explain how information gaps were addressed; and 4) explain the rationale behind the user's risk management decisions and actions.

The amount of information required in the framework is directly related to the potential extent and degree of exposure of the specified application. ED and DuPont recommend that a broad range of stakeholders have access to the worksheet or summaries of it as products move into commercialization in order to facilitate ease of understanding. DuPont has made it clear that it fully supports this framework. In fact, DuPont has made the framework standard for its own operations involving nanomaterials. In at least one instance, applying the framework indicated that a product's development should be halted (Fisher 2007).

2.7 Pros and cons of existing tools and frameworks

In Table 2 we have summarized the key characteristics of the various tools, approaches and frameworks in regard to focus, methods, hazard and exposure evaluation input parameters, risk evaluation and risk handling, etc. as well as their pros and cons in regard to the scope of this project. When comparing the pros and cons of existing tools and frameworks it is important to note that such a comparative analysis can never do full justice to the all tools and frameworks. The methods, approaches and frameworks presented here are all helpful in to the primary evaluation of the potential hazards, exposures and risks related to production and application of nanomaterials although they might not all be equably helpful in relation to meeting the purpose of this project. Many of the tools such as e.g. Genaidy ***et al.*** (2009) and the Nanorisk framework (ED & DuPont 2007) are developed in order to help developers and producers of nanomaterials complete crude risk estimations. Whereby the hope is that this will make developers and producers focus on minimizing exposure or facilitate the implementation of various more or less stringent control measures to protect workers in the primary production and handling of nanomaterials. Only some of the methods and frameworks (e.g. the Swiss Precautionary Matrix and the MCM risk-based classification system) involve professional end-users, consumers and the environment which are the subject of this project.

Although varying greatly in focus and scope, most of the approaches and frameworks provide guidance on how to make a crude assessment of the hazards and exposure associated with a nanomaterials and its use(s). In re-

gard to the hazard of nanomaterials, all but the framework proposed by Genaidy ***et al.*** (2009) set up a series of criteria or hazard endpoints that have to be considered. It is however not always clear why a given criteria was included or excluded from the analysis. Furthermore, some of the criteria are based on mass, which many of the authors of proposed frameworks themselves state is not sufficient to deal with nanomaterials. Among other the Swiss Precautionary Matrix, the MCM risk-based classification system and CB Nanotool assign numbers or ranges to the extent of various reported effects, which makes the frameworks easy and transparent to use in the sense that these numbers are assigned to various effects by default and the scoring process can be validated by others. How the numbers or ranges have been assigned to the various effects is less transparent.

In regard to exposure of nanomaterials, most approaches and frameworks use an estimate of the likelihood of exposure or a more-or-less precise relative scale. These are useful to identify activities with potential risks of exposure, as it has been shown with the completely qualitative model proposed by Genaidy ***et al.*** (2009). A weakness of these tools is however that they do not provide a strong tool for estimating an actual exposure level. It could be a great help to identify whether for instance a high likelihood for exposure also gives cause to a "high exposure". Control Banding Nanotool provides the possibility of assessing the exposure level based on the amount of material handled and the frequency of the activity. The English system developed by BSI and the Swiss Precautionary Matrix use either a simple assessment or actual exposure measurements. Actual exposure measurements require the use of a series of fairly complex measurement methods to estimate the fraction of the nanomaterial that become airborne at the workplace. The development of quantitative model would make it possible to complete solid exposure assessments before nanomaterials are used in a large scale. New methods are under development and hopefully they will help solve some these problems, but there is a long way in areas like consumer exposure and environmental exposure modelling before we reach the level of the models that are now available for assessing human to fine and ultrafine particles.

Combining the hazard and the exposure assessment, all of the tools and frameworks derive an overall score, which is then again linked to a categorization e.g. A, B, C, or high, medium, low. The categorization makes the results of using the tool easy to summarize and communicate on the one hand, but also risks masking the process by which the categorization was derived. Thereby the scientific analysis of the available evidence of human and environmental hazards goes in the background as so does the line of argumentation used to derive the overall score and subsequent categorization. A number of frameworks translate the overall score into a set of recommendations for general prescribed management measures. Such an approach is e.g. explored in the Swiss Precautionary Matrix and the CB Nanotool. In order for these recommendations to be generic they have to be very broadly defined, which risks making them too general and non-specific to give input to real decision support.

Common for most of the concepts available today is that their input data requirements are fairly high and some of the scientific information needed in order to apply them is inconclusive at the moment or non-existing. Lack of information and data is the reality even for the nanomaterials that are applied in high quantities today.

Some of the concepts are furthermore based purely on theoretical considerations and time-consuming to apply in reality. This underlines the importance of developing a new, step-wise and more transparent decision-making tool to evaluate the exposure and hazards of nanomaterials to human health and the environment. It is however important to learn from these concepts and learn from the experiences made with these, in order to make sure that a new decision-making tool is up-to-date, transparent, and applicable.

Table 2: Summary of the main characteristic of the different frameworks

Name	BSI Nanomaterials Handling Guide	CB Nanotool	Swiss Precautionary Matrix
Reference	BSI (2007)	Paik *et al.* (2008)	Höck *et al.* (2008)
Focus/ Applicability	Work environment	Work environment	Workers, consumers, environment
Scope	Nanoparticles	Nanoparticles	Nanoparticles and nanorods
Method	Qualitative/quantitative	Qualitative/quantitative	Qualitative/quantitative
Strategy	Hazard evaluation + Exposure assessment + Handle risk	Hazard evaluation Exposure assessment + recommended risk handling	Hazard evaluation + Exposure assessment+ Assessment risk handling need
Exposure assessment input parameters	1)Describe work procedure 2) Who is exposure? 3) What is the exposure route (inhalation, oral, dermal)? 4) When does exposure occur? 5) Frequency of exposure 6) Level and extent of exposure[8] 7) Source of exposure potential 8) Protection possibility	1) Determine number of employees in completing the activity 2) Frequency of the activity 3) Time extend of activity 4) Amount of nanomaterial used in each cycle of the activity 5) Dustiness index or evaluation of mistiness	1) Type of exposure (air, liquid or in a matrix)? 2) Amount of nanomaterial a worker normally exposed to during a day? 3) How much nanomaterial can a worker be exposed to in a worst case?
Scale assessment of exposure level	Assess (estimate) or do measurements	Linear 4-step scale calculated based on points given for the five exposure parameter/ measurements	For airborne exposure the risk is scaled by the 2 remaining parameters under normal circumstances and accidents
Hazard evaluation input parameter	CMAR Fibrous Insolble Soluble	Surface chemistry Particle shape Particle diameter Solubility CMAR(nano- and bulk materials) Dermal toxicity (nano- and bulk materials) Occupational Exposure Level	Redox activity and/or catalytic activity Stability in physiological and environmental conditions
Scale evaluation of hazard evaluation	None	1) Assign severity factors btw 0-10 p., 2) derive overall score btw 0-100 p., 3) assign probability estimate (0-100)	Input parameters are scored btw 1-9
Risk evaluation	Categories into the 1) most serious risks to health; 2) risks that are likely to occur soonest; and 3) risks that can be dealt with soonest	Combine severity score and probability score into four possible risk levels (RL)	Total score of the precautionary need V = N * (W * E + S) and classified as "A" (V= 0-20) and "B" (V> 20)
Risk handling	"Hierarchical risk handling" based on COSHH principles	Control bands and exposure control	Unspecified
Special circumstances	Nanomaterial specific maximum exposure standards	Unknown parameters is assigned 75 % of the maximum score	Nanoscale is extended to 500 nm; Unknown parameters is assigned 100% of the high risk score; Actual/estimated daily or worst case inhalation exposure – and not material quantity
Pros	Pro-active in the sense that risk handling can be implemented immediately	High usability, Pedagogical color code, clear results that limit "paralysis by analysis"	Step-by-step guide is clear and easy to apply; considers workers, consumers, environment as well as taking a life-cycle perspective
Cons	Relies on having good information about the hazardous nature of materials, the effectiveness of control approaches and convenient and accessible ways to monitor exposure. This information might not always be available	Unclear how severity scores and probability were assigned e.g. to particle shape and dustiness and not clear why unknown parameters is assigned 75 % of the maximum score	Questionable use of default values for the redox activity or catalytic activity; Unclear why unknown parameters is assigned 100% of the high risk score; Questionable quantitative derivation of whether there is a precautionary need for action; Overall classification scores seems arbitrary

Table 2: Summary of the main characteristic of the different frameworks continued

Name		**Nanorisk framework**	**MCM risk-based classification**
Reference	Genaidy *et al.* (2009)	ED & Dupont (2007)	Tervonen *et al.* (2009)
Focus/ Applicability	Work environment	Workers, consumers, environment	Human and environment
Scope	Nanomanufcaturing operation	Nanoapplications and products	Nanoparticles
Method	Quantitative	Qualitative/quantitative	Qualitative/quantitative
Strategy	Hazard evaluation + Exposure assessment + Handle risk	Describe, evaluate and decide, update and re-execute life-cycle hazard-, exposure- and risk profiles	Select and define criteria, identify options, rank options in regard to criteria, select optimal option(s)
Exposure assessment input parameters	Not specified	Among other: 1) Number and locations of manufacturing sites 2) Current and expected production 3) Industrial function 4) Maximum concentration used 5) required controls, etc.	Not applicable
Scale assessment of exposure level	Logarimic 5-step scale (US DOD *Mishap probability levels")*: Frequent, Probable, Occasional, Remote, Improbable	Not specified	Not applicable
Hazard evaluation input parameter	Not specified	Short-term tox, skin sensitization/irritation, skin penetration, genetic toxicity tests, biological fate and behavior, chronic inhalation/ingestion /dermal tox studies, Developmental and reproductive toxicity studies, Neurotox studies, genotox studies and endocrine-disruption studies	Agglomeration and aggregation, reactivity, critical functional groups, particle size, and contaminant dissociation, size, bioavailable and bioaccumulation potential and toxic potential
Scale evaluation of hazard evaluation	Catastrophic (Deaths); Critical (Severe injuries or illness); Marginal (Minor injury or illness); Negligible (No illness or injury)	Not specified	Particle size evaluated as the mean size of the material in units of nanometers and expert estimates. All other criteria were scored from 1 to 5 via expert judgment. 1 was the most favorable (least risk), while 5 the least favorable (highest risk).
Risk evaluation	A risk code is determined depending on the probability–severity values. There are five risk levels e.g. "Very high" or "red"; "High" or "orange", etc.	Evaluate nature, magnitude and probability of risk types	Classification into extreme, high, medium, low, and very low risk categories
Risk handling	Haddon's system	Focused on minimizing exposure	Unspecified
Special circumstances	For each of the intervention strategies four criteria were applied: applicability, benefit, cost and feasibility	Sharing of product info, hazard, exposure and risk profiles with stakeholders is recommended	Uses an outranking model termed Stochastic multicriteria acceptability analysis (SMAA-TRI)
Pros	Scenarios are illustrated as activity appellations without any further description of the circumstances	Clear guide on how to organize, document, and communicate information	High level of transparency in selection of criteria and enables the users to define their own criteria
Cons	Unclear hazard input parameters and assignment of risk codes	High data requirements often not available, unclear how to evaluate nature, magnitude and probability of risk types, independent validation by stakeholders hard	Low level of transparency in the qualitative assignment of scores between 1 and 5 to various nanomaterials. Unclear how specific weight bonds were assigned

3. NanoRiskCat

It is the aim that NanoRiskCat will enable companies, regulators and independent parties to identify, categorize, rank and communicate any eventual risk associated with the specific application(s) of a given nanomaterial by sequentially mapping and reporting in the:

1. Exposure potential for professional end-users
2. Exposure potential for consumers
3. Exposure potential for the environment
4. A preliminary hazard evaluation for humans
5. A preliminary hazard evaluation for the environment

A generic template for mapping and reporting these five aspects for a specific application of a given nanomaterial has been developed and can be found in Appendix 1 of this report. In its simplest form the final outcome of using NanoRiskCat for a nanomaterial in a given application will be communicated in the form of a short title describing the use of the nanomaterial (e.g. MeO in ship paint) and five color-coded dots (e.g. ●●●|●●). The first three colored dots refer to potential exposure of professional end-users, consumers and the environment, respectively, whereas the last two colored dots refer to the hazard potential for humans and the environment, respectively. The dots can have four different colors assigned to them by the user of NRC: Red (●), yellow (●), green (●) and grey (●). The red, yellow and green colored dots respectively indicate high, medium and low indication of exposure or effect whereas the grey indicates that the data available is too limited to assess the possibility for exposure or effect.

The color coding principle in NanoRiskCat is shown in the table 3 below:

Table 3: Color coding principle in NanoRiskCat. Assignment of colors is based on the methodology provided in Chapter 3.2 (exposure potential for professional users, consumers, and the environment), 3.3 (human health effects), and 3.4 (environmental effects).

Exposure indication			**Effect indication**	
Professionals	**Consumers**	**Environment**	**Human health**	**Environment**
<color> ●	<color> ●	<color> ●	<color> ●	<color> ●
			<sentence from list below>[a)]	<sentence from list below>[b)]

[a)] Refer to a list of default sentences that can help NRC users to communicate on which kind of evidence the color coding for human health hazard is based (see Appendix 2, Table A2.1)

[b)] Refer to a list of default sentences that can help NRC users to communicate on which kind of evidence the color coding for environmental hazards is based (see Appendix 2, Table A2.2).

Box 1. Example of the use of NanoRiskCat for categorization of the exposure and hazard potentials of two different nanomaterials used in ship paints (hypothetical cases)

For the use of two different nanomaterials (hypothetical materials denoted MeO and FO) in ship paints the following two NanoRiskCat profiles may be obtained

MeO in ship paint

Exposure			Effects	
Professionals	**Consumers**	**Environment**	**Human health**	**Environment**
●	●	●	●	●
			4[a)]	6[b)]

a) "based on bulk CLP classification 1 or 2 for carcinogenicity"
b) "based on bulk CLP classification of Chronic 3 or Chronic 4 and $T_{1/2}$ > 40 d"

FO in ship paint

Exposure			Effects	
Professionals	**Consumers**	**Environment**	**Human health**	**Environment**
●	●	●	●	●
				12[b)]

b) "based on bulk CLP classification of Chronic 3 or Chronic 4 and an evaluation of dispersive or long range transport, ecosystem effects and novelty"

Red, yellow and green colored dots indicate high, medium and low indication of exposure or effect whereas the grey indicates that the data available is too limited to assess the possibility for exposure or effects. Hence in the first case there is a medium indication of exposure towards professional end-users and consumers, whereas the indication of environmental exposure is expected to be high. The indications of effects from the nanomaterial as such in relation to both human and the environment are expected to be high.

In the second case the exposure profile is the same as in the first case, but the indication of adverse effects on humans is low and there is insufficient knowledge and data to evaluate the possibility of environmental effects.

The two examples consider the same use and form of application and the exposure profiles are therefore the same for the two materials (i.e. ●●●). A comparative analysis of the hazard profile of the two materials would suggest that it is preferable or "more safe" to use FO in ship paint. This is due to the human hazard profile for MeO is "red" vs. "green" for FO whereas the environmental hazard profile for MeO is "red" vs. "grey" for FO. However, to make such final conclusion it is necessary to take account of the respective concentrations of the nanomaterial in the products, the hazardous properties and the concentration of the other constituents in the products and whether there are any differences in the handling and the exposure potential between the products. Thus the screening tool gives an indication that has to be further verified before a final decision can be made.

The purpose of the development of NanoRiskCat is to create a generic framework, which can be applied for specific application(s) of specific nanomaterial(s). Although NanoRiskCat is a qualitative tool, quantitative values should and can be applied in the criteria setting for the assignment of color code.

It is important to underline that NanoRiskCat is not a product label and NanoRiskCat is only to be used for evaluating the nanomaterial as an ingredient under the physical conditions it occurs in the product (e.g. in a liquid suspension or embedded in a solid matrix). For example, the use of nanoscale titanium dioxide in sun lotion or in varnish products, cerium oxide used as a diesel additive, or nanosilver in textiles can be evaluated using NanoRiskCat in a generic way, thus NanoRiskCat is applicable for all types of commercial products. However NanoRiskCat does not take account for the exposure and hazard for the other constituents in the product, nor the additives or impurities. NanoRiskCat is directed towards the generic use descriptors and scenarios, which for instance are apparent in the product categories used in REACH. Thus, NanoRiskCat furthermore does not consider whether the content of the nanomaterial is low or high in the product nor does it evaluate exposure and hazard from the other constituents and impurities in the product, as such an evaluation would require exposure scenario specific risk assessments for the substances included in the products according to the conventional methodology described in REACH.

It is the hope that NanoRiskCat will contribute to the safe handling of nanomaterials in specific applications and it is important to underline that filling out NanoRiskCat cannot be used to pass judgment about the safety of all applications of a given nanomaterial.

While information on inherent physico-chemical and biological properties is needed to complete full hazard identification, it has to be recognized that there is a general lack of information on nanomaterials and thus many unknowns exist. A screening tool that takes outset in the requirements for performing traditional risk assessment (i.e. hazard identification derived from inherent physico-chemical properties followed by exposure and effects assessments) would therefore in most cases fall short and end up in a conclusion that additional input data are required. This counteracts the desire for providing timely guidance to companies, regulators and interested parties based on available data.

Therefore a fundamental principle of NanoRiskCat is to exploit existing knowledge and data to the full extent possible in an approach that assesses which applications of nanomaterials that, on a relative scale, are more problematic than others.

This is done by adapting the traditional paradigm in risk assessment of chemical substances, i.e. risk expressed as the relationship between hazard and exposure, in such a way that a qualitative exposure evaluation (for defined subgroups i.e. professional end-users, consumers and the environment) is performed before traditional hazard identification is carried out. Focus is on establishing the exposure potential based on the assumption that we know a lot more about the application of nanomaterials in various products than we do about their fate in the environment and their toxicological and ecotoxicological hazard potentials.

This principle has also previously been identified by the British Standardization Institute (BSI, 2007), who stated that:

"***The likelihood (or risk) of disease occurring depends on the dose of the particles in the organ where disease can occur, and the toxicity of nanoparticles. (…) If there is no exposure (i.e. no nanoparticles in the air), no dose will accumulate and, despite the potential toxicity of the particles, there will be no risk to health. It therefore follows that an appropriate response to the risks from nanomaterials is to understand the potential exposures which could arise from the manufacture and use of nanomaterials and to put in place measures to mitigate, manage or reduce exposure. In this way the risks can be controlled.***" (BSI 2007)

For each application of a specific nanomaterial, the use of NanoRiskCat has to describe the specific nanomaterial produced and/or used, specify use scenario(s), and complete an evaluation of the exposure potential professional end-users, consumers and the environment as well as, if possible, establish a toxicological and ecotoxicological hazard profile of the specific nanomaterial. The short title describing the use of the nanomaterial (chapter 3.1) combined with the exposure (chapter 3.2) and the hazard profile (chapter 3.3) will give a color code that summarizes the hazard profile of the specific application of the nanomaterial. Each of these elements will be introduced in the following.

3.1 Short titles for use scenario(s) and nanomaterial identification

In order to provide an evaluation of the hazard profile and provide an evaluation of the exposure potential for professional end-users, consumers and the environment background information on the nanomaterial(s) and its specific use(s) is needed.

First of all, the NanoRiskCat subject should be clearly specified in the form of a short title, defining the specific kind(s) of nanomaterial(s) under analysis and their use(s). This should be communicated in the form a short title describing the use of the nanomaterial. The short title could be general e.g. "TiO_2 nanoparticles used in sunscreens" or very specific e.g. (hypothetical example) "40 nm rutile TiO_2 nanoparticles used in Engima SunProtection Factor 50". The important thing is that it is clearly stated which nanomaterial and which use/application is subject for the evaluation. Schemes for reporting such information already exist, for instance NANOSAFER developed by National Research Centre for the Working Environment and Danish Technological Institute (Industriens Branchearbejdsmiljøråd 2011) or the Nano Risk framework developed by Environmental Defense and DuPont (2007) (see "Section 1: Describe Material and Its Applications").

Second, some basic information and consideration is needed regarding the production of the nanomaterial and the products containing the specific nanomaterial as well as known use(s) and expected route of disposal routes of the products containing the nanomaterial. This includes information about the nanomaterial in its pristine form as well as in the form it is used by consumers and/or professional end-user. Information must be provided on at least: the known professional and non-professional uses of the product, release information, information about who handles a product at what stage of its use(s) and applied and/or required personal protection equipment (PPE). A

schematic overview of key elements in the life cycle of the nanomaterial in the specific use scenario may also be provided. Guidance on how to complete such an analysis can be found in Section 2: Profile Lifecycles of the Nanorisk framework developed by Environmental Defense and DuPont (2007), see Table 3 below.

Table 3: Table to be filled in for identification of material life-cycle stage in the given application. Adapted from "Section 2: Profile Lifecycles" of the Nanorisk framework developed by Environmental Defense and DuPont (2007).

Material life-cycle stage	Description
Material Sourcing (e.g. producer, supplier)	<to be filled in by the user>
Manufacturing (e.g. processing, product fabrication, filling/packaging)	<to be filled in by the user>
Distribution	<to be filled in by the user>
Use/maintenance/reuse	<to be filled in by the user>
Disposal/Recycling	<to be filled in by the user>

3.2 Criteria for evaluating the exposure profile

Based on the information provided in the previous section, the exposure potential for professional end-users, consumers and the environment should be assessed and assigned a color code accompanied by a clear explanation of why the chosen color reflects what is currently known about exposure.

Specific knowledge about the exposure situation is of course first choice for the exposure evaluation. Where such information is not available the generic approach sketched here should be used to evaluate the exposure potential for professional end-users, consumers and the environment. The exposure evaluation in NanoRiskCat takes outset in the use descriptor system established by ECHA in the current REACH Guidance on information requirements and chemical safety assessment Appendix R.12 (ECHA 2010). In brief, the use descriptors are those categories of use that the producer or importer of a substance has registered the compound in, i.e. what is the substance going to be used for? There are five separate lists of descriptors with a number of sub-categories, but not all the various categories are equally relevant for professional end-users, consumers and the environment when it comes to nanomaterials. Table 4 lists the use descriptors recommended in NanoRiskCat.

Table 4: Overview of relevant use descriptor for an evaluation of potential exposure of professional end-users, consumers and the environment in NanoRiskCat. Use descriptors are selected among those listed in ECHA (2010).

Use Descriptor Categories in REACH	Prof. end-users	Consum-ers	Environ-ment
Process (PROC)	X		
Product (PC)	X	X	
Technical functions (FC)	X		
Article, no intended release (AC)	(X)	(X)	X
Articles, intended release (AC)	(X)	X	X
Environmental Release (ERC)			X

For each use category, a color code (●, ●, ● or ●) has been assigned based on 1) the location of the nanomaterial (bulk, on the surface, liquid or airborne) and 2) a judgment of the potential for nanomaterial exposure based on the description and explanation of each process, product category, technical function, article and environmental release category provided in the REACH Guidance. Tables of use categories and the default color codes assigned to each use category are shown in Appendix 3.

As mentioned above, this categorization is based partly on the description and explanation associated with each process (PROC), product category (PC) and technical functions (FC), etc. and partly on an assessment of the exposure potential of the use of a given nanomaterial used in a specific process, product and/or technical function following the framework developed by Hansen ***et al.*** (2007, 2008). The framework developed by Hansen ***et al.*** (2007, 2008) is based on categorizing nanomaterials according to location of the nanomaterial (see Figure 1) and grouping applications of nanomaterials into four different exposure categories:

1. expected to cause exposure
2. may cause exposure
3. no expected exposure
4. unclassifiable due to lack of information

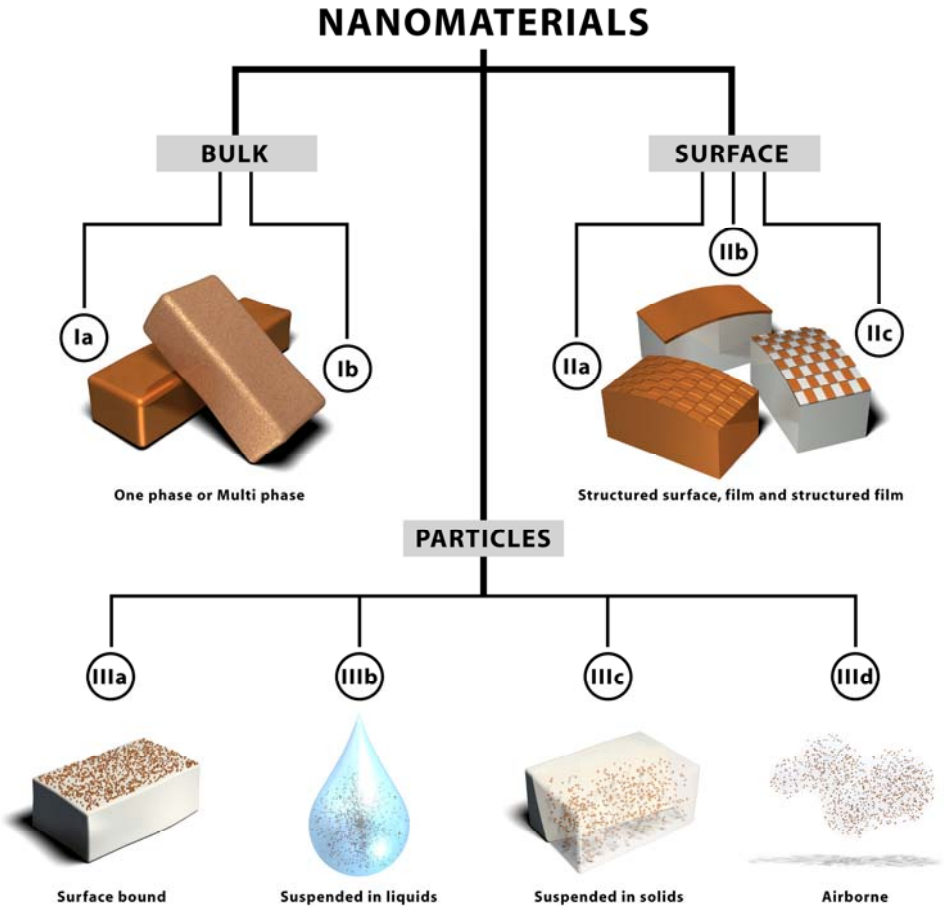

Figure 1. The categorization framework for nanomaterials. The nanomaterials are categorized according to the location of the nanostructure in the material (Reprinted from Hansen *et al.* 2007).

Guidance on how to determine the location of the nano-element can be found in Hansen ***et al.*** (2007) and Hansen ***et al.*** (2008). In short, Hansen ***et al.*** (2007) suggest categorizing nanomaterials depending on the location of the nanoscale structure in the system. This leads to a division of nanomaterials into three main categories:

1. materials that are nanostructured in the bulk;
2. materials that have nanostructure on the surface and;
3. materials that contain nanostructured particles.

As a general rule processes, products and technical functions which involve ‘‘nanoparticles suspended in liquids’’ or ‘‘airborne nanoparticles” exposure is to be expected. Hence these use categories have been given a color code of red (●). If they involve ‘‘surface-bound nanoparticles’’ and hence may cause exposure, a color code of yellow (●) has been given and finally, if they involve “nanoparticles suspended in solids” for which exposure is not expected they have been assigned a color code of green (●) (see Figure 2).

Although it seems unlikely, it should be recognized that there maybe some products for which the professional end-users or the users of NanoRiskCat do not know or cannot determine the location of the nano-element in the product and hence cannot determine the exposure potential. In such cases, the product would fall into the fourth category due to lack of information, with an associated grey color-code (●).

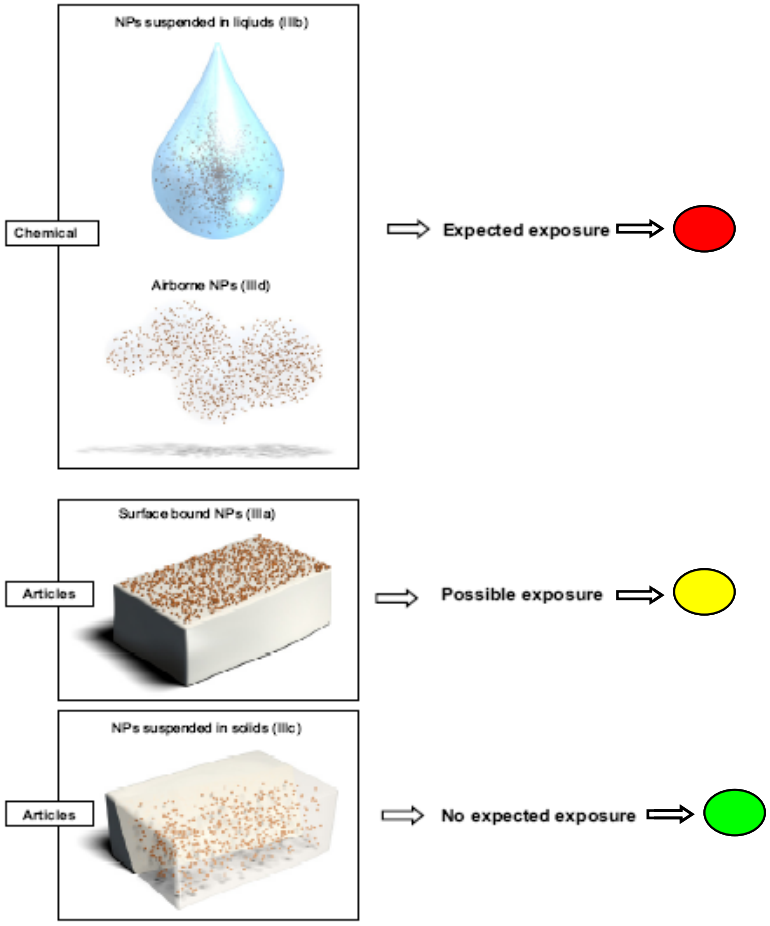

Figure 2. Generic approach used in NanoRiskCat to assign the color-code to products with no, possible and expected exposure depending on the location of the nanomaterial in the product (adapted from Hansen *et al.* 2008c)

3.2.1 Evaluating the potential exposure for professional end-users

The first part of the exposure evaluation in NanoRiskCat focuses on the evaluating the exposure potential for professional end-users of a nanomaterial containing product. Evaluating the exposure potential for workers in the production chain of nanomaterials is beyond the scope of this framework, but guidance on how to address this issue can be found in among other NANOSAFER (Industriens Branchearbejdsmiljøråd 2011) and in Genaidy ***et al.*** (2009).

The evaluation of the potential exposure for professional end-users is based on REACH Guidance on information requirements and chemical safety assessment Appendix R.12:

- 27 Process categories (PROC) e.g. PROC 1= Use in closed process, no likelihood of exposure (•), PROC 7= Industrial spraying (•), PROC 10= Roller application or brushing (•)
- 40 Chemical Product Categories (PC) e.g. PC 1= Adhesives, sealants (•) and PC 2= Adsorbents (•)
- 51 functional categories (FC) a substance may have in a chemical product or article e.g. FC 1= Aerosol propellants (•) and FC 4= Anti-freezing agents (•) (ECHA 2010)

This, for instance, leads to the color code of green being assigned to PROC 1 since in this process categories are defined by "Use in closed process, no likelihood of exposure". The color code of red is assigned to PROC 7 since the examples and explanations column states "Air dispersive techniques" and "Substances can be inhaled as aerosols". Applying this approach would mean for instance that Chemical Product Category called "Air care products" (PC 3) would be "red" since it is assumed that the nanomaterial will have to be suspended in liquids and/or may become airborne and hence exposure is to be expected. Finger paint (PC 9c) would also be classified as "red" since it is assumed that nanomaterials used in finger paint would have to be suspended in liquids and there is direct dermal exposure. It should be noted that personal protection equipment is not included in the consideration of the potential of worker exposure.

As the exposure potential is expected to vary over the course of the use phase of the product, only the highest exposure potential for professional end-users should be reported as the first dot in NanoRiskCat.

The color code assigned to the various PROCs, PCs and FCs should be used as the default colors that should be reported as the first dot in NanoRiskCat. Deviation of the default color assigned to each PROCs, PCs and FCs would have to be elaborated on and explained and justified in a reasonable and transparent manner by the user of NanoRiskCat. The list of PROCs, PCs and FCs are not meant to be regarded as a complete list and other uses should be described as appropriate and given a color code by the user of the NanoRiskCat with due explanation.

3.2.2 Evaluating the potential exposure for consumers

As in the case of professional end-users, the evaluation of the potential exposure for consumers is based on ECHA's REACH Guidance on information requirements and chemical safety assessment Appendix R.12:

- 40 Chemical Product Categories (PC), e.g. PC 1= Adhesives, sealants (•) and PC 2= Adsorbents (•)
- 13 Article categories (AC), no release intended (AC), e.g. AC 1= Vehicles (•)
- 8 Use descriptors for articles with intended release of substances, e.g. AC 31= Scented clothes (•)

As in the case of professional end-users a color code has been assigned to each use category (see Appendix 3) depending on the location of the nanomaterial and a judgment of the likelihood of consumer exposure of a given nanomaterials being used in a product or article that falls into each of these chemical product and article categories. This judgment is based partly on the description and explanation associated with each PC and AC and partly on an estimation of the exposure potential of the use of a given nanomaterial used in a product and/or article following the framework developed by Hansen ***et al.*** (2007, 2008).

As the exposure potential is expected to vary over the course of the use phase of the product, only the highest exposure potential for consumers should be reported as the second dot in NanoRiskCat.

This color code could then be the default color that should be reported as the second dot in NanoRiskCat. Deviation of the default color assigned to each Chemical Product Category would have to be elaborated on and explained and justified in a reasonable and transparent manner by the user of NanoRiskCat.

3.2.3 Evaluating the exposure for the environment

As in the case of professional end-users and consumers, evaluating the exposure for consumers is based on ECHA's REACH Guidance on information requirements and chemical safety assessment Appendix R.12:

- 13 Article categories (AC), no release intended (AC) e.g. AC 1= Vehicles (●)
- 8 Use descriptors for articles with intended release of substances e.g. AC 31= Scented clothes (●)
- 12 Environmental Release Categories (ERC) e.g. ERC 1= Manufacture of substances (●) , ERC 2= Formulation of preparations (●), and ERC 12b= Industrial processing of articles with abrasive techniques (high release) (●)

As in the case of professional end-users and consumers, a color code has been assigned to each Environmental Release Category (see Appendix 3.6) depending on the location of the nanomaterial and our judgment of the likelihood of environmental exposure of a given nanomaterial that falls into each of these categories. This judgment is based partly on the description and explanation associated with each PC and AC and partly on an estimation of the exposure potential of the use of a given nanomaterial used in a product and/or article following the framework developed by Hansen ***et al.*** (2007, 2008). Using this approach, ERC 1 would be assigned a color code of yellow whereas ECR 8D and ERC 10B would be assigned the color red.

As the exposure potential is expected to vary over the course of the use phase of the product, only the highest exposure potential for the environment should be reported as the third dot in NanoRiskCat. Deviation of the default color assigned to each category would have to explained and justified in a reasonable and transparent manner by the user of NanoRiskCat. There are furthermore a few ERC (i.e. ERC 4 and ERC 6a) for which a default color code could not be assigned and in such cases it is up to the user of NRC to assign the most appropriate color code to their uses.

3.3 Criteria for evaluating the potential human health hazards

The tiered approach was developed to assign a color to the human health hazards to a given nanomaterial as illustrated in Figure 3. When assigning a color to the dot representing potential human health hazards (dot number four) of a given nanomaterial the following indicators/qualifiers should be considered:

1. Does the ***nanomaterial*** fulfil the HARN[7] paradigm?

[7] HARN refers to High Aspect Ratio Nanoparticles indicating that the nanoparticles have a length to diameter aspect ratio greater than 10 to 1. Furthermore, it is required that: 1) The diameter of the fibres must be thin enough pass ciliated airways; 2) the

2. Is the ***bulk form*** of the nanomaterial known to cause or may cause serious damaging effects, i.e. is the bulk form classified according to the CLP[8] with regard to one or more serious health hazards such as germ cell mutagenicity, carcinogenicity or reproductive toxicity in category 1A, 1B or 2?

3. Is the ***bulk form*** of the nanomaterial classified for other less severe adverse effects according to the CLP such as skin corrosion/irritation category 2 and specific target organ toxicity-single exposure category 3?

4. Is the specific ***nanomaterial*** known to be acute toxic?

5. Are there indications that the ***nanomaterial*** causes genotoxic, mutagenic, carcinogenic, respiratory, cardiovascular neurotoxic or reproductive effects in humans and/or laboratory animals or has organ-specific accumulation been documented?

The background for each of these criteria will be explained and elaborated on in the following section. For each of these questions, reasoning should be provided with proper referencing to the scientific and/or non-scientific literature and an answer of each of the question should be provided in the form of either: yes, maybe, no, or no information. The answer "yes" implies that there is conclusive evidence or data giving cause to substantial concern that the nanomaterial in question may cause ir-/reversible effects (e.g. carcinogenicity) or that the nanomaterial holds a given property (e.g. persistency). "Maybe" indicates that data is not conclusive but gives cause to some concern, whereas "no" indicates that there is conclusive evidence that indicates that the nanomaterial does not cause adverse ir-/reversible effects and/or hold the properties in question. No data indicates that no or very limited and insufficient data is available for hazard evaluation.

While in principle none of these questions are more important than others, Figure 3 gives a guidance on the order in which they may be evaluated and a short description of the criteria to be used. Below follows a more detailed description of each indicator and the cut-off values chosen.

The red color code in Figure 3 signifies that indications of adverse effects are high; the yellow signifies that indications of adverse effects are medium, and green that indications of adverse effects are low. Grey should be used if there are numerous data gaps and unknowns to warrant no conclusion to be made about the human hazards of the nanomaterial. Transparency in the assigning of a color code is key and very important. Therefore, all categorizations made based on Figure 3 must be accompanied by an explanatory text on how the conclusion was reached (as shown in the cases in Chapter 4).

NanoRiskCat is a tiered approach in the sense that once a color code has been

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length must be long enough to initiate the onset of e.g. frustrated phagocytosis and other inflammatory pathways; and 3) the nanomaterials must be biopersistent (Tran ***et al.*** 2008).

[8] Regulation (EC) No 1272/2008 of the European Parliament and of the Councul of 16 December 2008 on classification, labelling and packaging of substances and mixtures, amending and repealing Directives 67/548/EEC and 1999/45/EC, and amending Regulation (EC) No 1907/2006

triggered (e.g. bulk materials CLP classified as an Acute toxic category 3 after oral exposure would trigger “red”), the nanomaterial cannot obtain a different color code (yellow, green or grey) even though the oral LC_{50} might be > 300 mg/l but 2000 mg/kg bodyweight.

It should be noted that the classification according to the Regulation (EC) No 1272/2008 on classification, labelling and packaging of substances and mixtures for the bulk material is used in the human hazard categorization in NanoRiskCat (EP and CEU 2008).

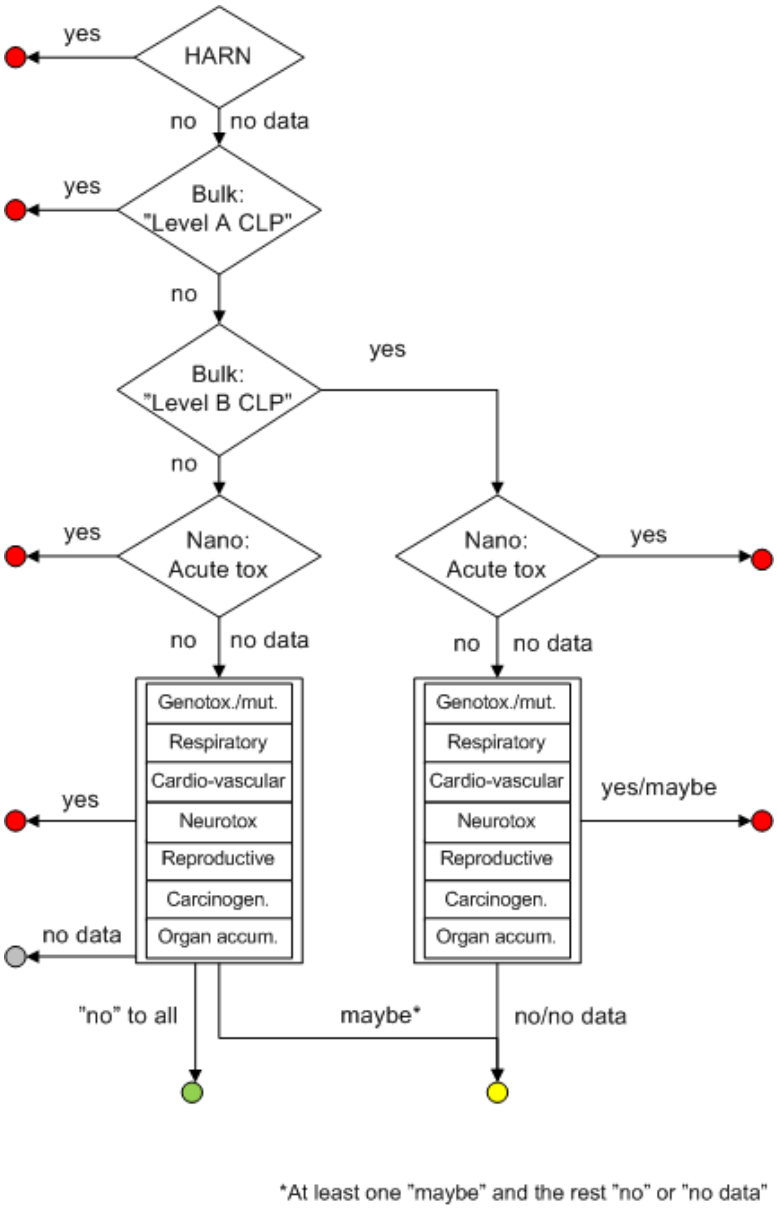

Figure 3. Road-map for assigning a human hazard colour code in NanoRiskCat. Red, yellow and green indicate high, medium and low indication of effect whereas grey indicates too limited data to make an assessment. For a guide to answering the questions, please refer to section 3.3.1 to 3.3.6.

3.3.1 HARN: Does the nanomaterial fulfill the HARN paradigm?

There is evidence that longer, durable or biopersistent fibres are more toxic by mass than shorter fibres of the same composition when inhaled. Animal studies suggests that fibres < 5 µm in length pose little risk of disease development, whereas 8 - 10 µm long fibers can cause mesothelioma and 10 - 15 µm produce disease in the lungs. (Meldrum 1996). The World Health Organization

has defined a fiber as being a particle of a length >5 µm, and a diameter <3 µm, and with an aspect ratio (length to diameter) of >3:1 (Meldrum 1996, BSI 2007).

In regard to nanomaterials specifically the so-called HARN-paradigm as been proposed by Tran ***et al.*** (2008). HARN refers to High Aspect Ratio Nanoparticles. In order to be classified as HARN the nanomaterials must have a high surface area and a length to diameter aspect ratio greater than 10 to 1. Furthermore, it is required that: 1) The diameter of the fibres must be thin enough pass ciliated airways; 2) the length must be long enough to initiate the onset of e.g. frustrated phagocytosis[9] and other inflammatory pathways; and 3) the nanomaterials must be biopersistent. Nanomaterials that would typically fulfil this paradigm would be e.g. carbon nanotubes, nanofibers, nanowires and nanorods (Tran ***et al.*** 2008). As shown in figure 3, an HARN classification will lead to a red color coding.

3.3.2 Bulk – "Level A CLP": Is the bulk form of the nanomaterial known to cause or may cause serious damaging effects?

The second question relates to the hazard characteristics of the bulk or parent version of a nanomaterial and if it is already CLP classified in regard to:

a) acute toxicity
b) skin corrosion
c) skin irritation
d) serious eye damage/irritation
e) respiratory and skin sensitization
f) germ cell mutagenicity
g) carcinogenicity
h) reproductive toxicity
i) specific target organ toxicity - single exposure
j) specific target organ toxicity - repeated exposure and
k) aspiration toxicity

This enables a broad identification of potential hazard (and a form of read-across) from a previously identified hazard associated with the material. In case the answer is "yes" a red color coding will be triggered if the CLP classification is one of the following:

1. Acute toxicity category 1-4
2. Germ cell mutagenicity category 1A, 1B or 2
3. Carcinogenicity category 1A, 1B or 2
4. Reproductive toxicity category 1 A, 1B or 2
5. Specific target organ toxicity - single exposure category 1 or 2
6. Specific target organ toxicity - repeated exposure and category 1 or 2
7. Aspiration toxicity category 1
8. Skin corrosion/irritation category 1A, 1B or 1C
9. Serious eye damage/irritation category 1
10. Respiratory and skin sensitization category 1

[9] Phagocyte failing to engulf its target whereby toxic agents from inside the phagolysosome can be released causing damage to healthy cells and tissue (Wikipedia 2011)

These classifications are termed “Level A CLP classifications”. The categorization of these CLP classifications as Level A is based on the CLP description of these hazard categories. For a substance or material to get one or more of the Level A CLP classifications they have to be either known or strongly suspected to cause severe and potentially irreversible harm.

In the case there is no CLP Level A classification association with the bulk form of the material, the answer to this question would be “no”, which again would trigger the need to go to the next step in the flow diagram in Figure 3. In case a nanomaterial does not have a bulk parent material (e.g. fullerene, nanotubes and organoclays) the answer to this question should be “no” by default.

3.3.3 Bulk – “Level B CLP”: Is the bulk form of the nanomaterial classified for other less severe adverse effects according to the CLP?

The third question again relates to the hazard characteristics of the bulk or parent version of a nanomaterial and whether it is suspected of causing one or more specific health hazards i.e. if the CLP classification is one of the following:

1. Skin corrosion/irritation category 2
2. Specific target organ toxicity-single exposure category 3
3. Serious eye damage/irritation category 2

These classifications are termed “Level B CLP classifications” and are considered to be less severe that Level A CLP classifications. The reasons that these CLP classifications are considered less severe is that the effects are described as reversible in the CLP hazard categories.

In case the answer is “yes”, the nanomaterials in questions can no longer be classified as “green”. In case a nanomaterial does not have a bulk form (e.g. fullerene, carbon nanotubes and organoclays), only the question about documented nano-specific effects has to be addressed.

3.3.4 Nano – Acute tox: Is the nanoform of the materials known to be acute toxic?

This question focuses specifically on what is known about the acute toxicity of the nanoform of the material. Acute toxicity is defined as adverse effects resulting from an oral or dermal administration of a single dose or multiple doses within 24 hours to a nanomaterial or an inhalation exposure of 4 hours (ECHA 2008, United Nations 2009).

Adverse effects could be clinical signs of toxicity, abnormal body weight changes, and/or pathological changes in organs and tissues, which in some cases may be lethal. Local irritation or corrosion of the gastro-intestinal tract, skin or respiratory tract following a single exposure are included here as well and the same goes for cellular level acute toxicity such as (i) general basal cytotoxicity (ii) selective cytotoxicity and (iii) cell-specific function toxicity (ECHA 2008).

As shown in Figure 3, a nanomaterial with a known acute toxicity will trigger a red color coding. The cut-off values chosen to determine the toxicity of a nanomaterial are similar to the acute toxicity hazard category 4 in CLP (EP and CEU 2008). For oral and dermal acute toxicity estimates (based on LD_{50}/LC_{50} when available), the acute toxicity cut-off has been chosen to be 2000 mg/kg. For dusts and mists (solid particles and liquid droplets in a gas) the acute toxicity estimate cut-off has been set to 5 mg/kg.

3.3.5 Are there indications that the nanomaterial causes genotoxic-, mutagenic, carcinogenic, respiratory, cardiovascular, neurotoxic or reproductive effects in humans and/or laboratory animals or has organ-specific accumulation been documented?

Question 5 focuses specifically on whether there are indications that the nanomaterial may cause either mutagenic, genotoxic, carcinogenic, respiratory, cardiovascular, neurotoxic or reprotoxic effects in humans and/or laboratory animals and whether organ-specific accumulation of nanomaterials have been documented.

As summarized in Stone ***et al.*** 2009 and Hougaard ***et al.*** (2010), there is compelling evidence that some nanoparticles may be associated with one or more of these end-points. Due to their severity, a response significantly over background in any of these endpoints results in a “red” classification.

For each of these endpoints, the user of NanoRiskCat has to review the literature and answer “yes”, “no” or “maybe” e.g. yes, there are indications that the nanomateirals is genotoxic.

Providing rigid rules for how to interpret the scientific evidence is not very meaningful, but as a general rule the answer would be "yes" if there are indications from epidemiological- and/or ***in vivo*** studies that indicate or confirm one or more of these effects.

In case of conflicting evidence from epidemiological- and/or in vivo studies, the answer to Question 5 could still be “yes” if there are one or more reasonable explanations for why one of the studies did or did not observed an adverse effect. The answer could similarly be “no” if there are one or more reasonable explanations (e.g. confounders) for why a study did observe an adverse effect while others did not. Finally, the answer would be “maybe” in cases where there is conflicting evidence and no reasonable explanations for why studies differ.

In regard to ***in vitro*** testing, it has been shown that these studies may not always accurately predict potential hazards of nanomaterials in more complex biological environments (CCA 2008) and hence indications of one or more adverse effects should be used either to discuss mechanisms of toxicity or in conjunction with other lines of evidence. In case no other lines of evidence are available, results stemming from ***in vitro*** can only be used to answer “maybe”, as positive or negative indications of effects are not considered convincing enough to answer “yes” or “no” at this point in time.

In case that the bulk form has no CLP classification and the answer is “no” to each for these effects, this would trigger a categorization as “green” whereas it would be “yellow” if the answer is “maybe” to at least one of the endpoints.

The alternate case is if the bulk form of the nanomaterial has a classified as a:

- Skin corrosion/irritation CLP category 2
- Specific target organ toxicity-single exposure CLP category 3
- Serious eye damage/irritation CLP category 2

In this case the fact that there are indicators that the nanomaterial might be associated with one or more nanospecific adverse effects as well would lead to classification as “red”. In case the bulk form has a level B CLP classification and there are no nanospecific adverse effects associated to it, would lead a classification as “yellow”.

In the case that no conclusion can be reached in regard to any of these effects, no categorization of the nanomaterial can be made this would lead a classification as “grey”.

3.3.6 Standard sentences associated with human health hazard classification as red, yellow and grey

To help communicate the scientific reasoning behind assigning a human health hazard classification and why a given nanomaterial was assigned red, yellow or grey, a number of standard sentences have been developed. These standard sentences are meant to reflect primarily whether the conclusion has been reached based on classification of the bulk form of the materials and/or ***in vivo*** or ***in vitro*** data on the nanomaterial and in regard to what endpoint. Depending to the final classification in regard to human health, the user of NRC has to select one or more of those sentences that best reflect the scientific basis for assigning the color code. A list of these sentences is given in Appendix 2, Table A2.1.

3.4 Criteria for evaluating the environmental hazard profile

In order to provide an initial estimate of the environmental hazards related to a given nanomaterial and its application and what is already known about the bulk form of the material, the following indicators/qualifiers should be considered:

1. Is the nanomaterial in question reported to be hazardous to environmental species?
2. Is the nanomaterial in question persistent?
3. Is the nanomaterial in question bioaccumulative?
4. Could use of the nanomaterial in question lead to potentially irreversible harm to the environment (e.g. ecosystem effects)?
5. Is the nanomaterial in question readily dispersed?
6. Is the nanomaterial in question novel?

For each of these questions, reasoning should be provided with proper referencing to the scientific and/or non-scientific literature and an answer of each of the question should be provided in the form of either: yes, maybe, no, or no information. The answer “yes” implies that there is conclusive evidence or

data giving substantial concern that the nanomaterial in question may cause ir-/reversible effects (e.g. mortality) or holds a given property (e.g. persistency). “Maybe” indicates that data is not conclusive but gives some concern for the effects in question, whereas “no” indicates that there is conclusive evidence that indicates that the nanomaterial does not cause adverse ir-/reversible effects and/or hold the properties in question. No data indicates that no or very limited and insufficient data is available for hazard evaluation. In principle none of these indicators are more important than others. As in the case of human health, Figure 4 gives guidance on the order in which they may be evaluated.

Short descriptions of the criteria to be used are given in sections 3.4.1-3.4.9. Outset is taken in existing criteria for chemicals with due consideration to the uncertainty related to ecotoxicological hazard of nanomaterials e.g. by changing the cut-off values for LC_{50} or EC_{50}. Below follows a more detailed description of each indicator and the cut-off values chosen. It should also be noted that the classification according to the European Regulation on classification, labelling and packaging of substances and mixtures (EP & CEU 2008) for the bulk material is used in the environmental hazard categorization in NanoRiskCat.

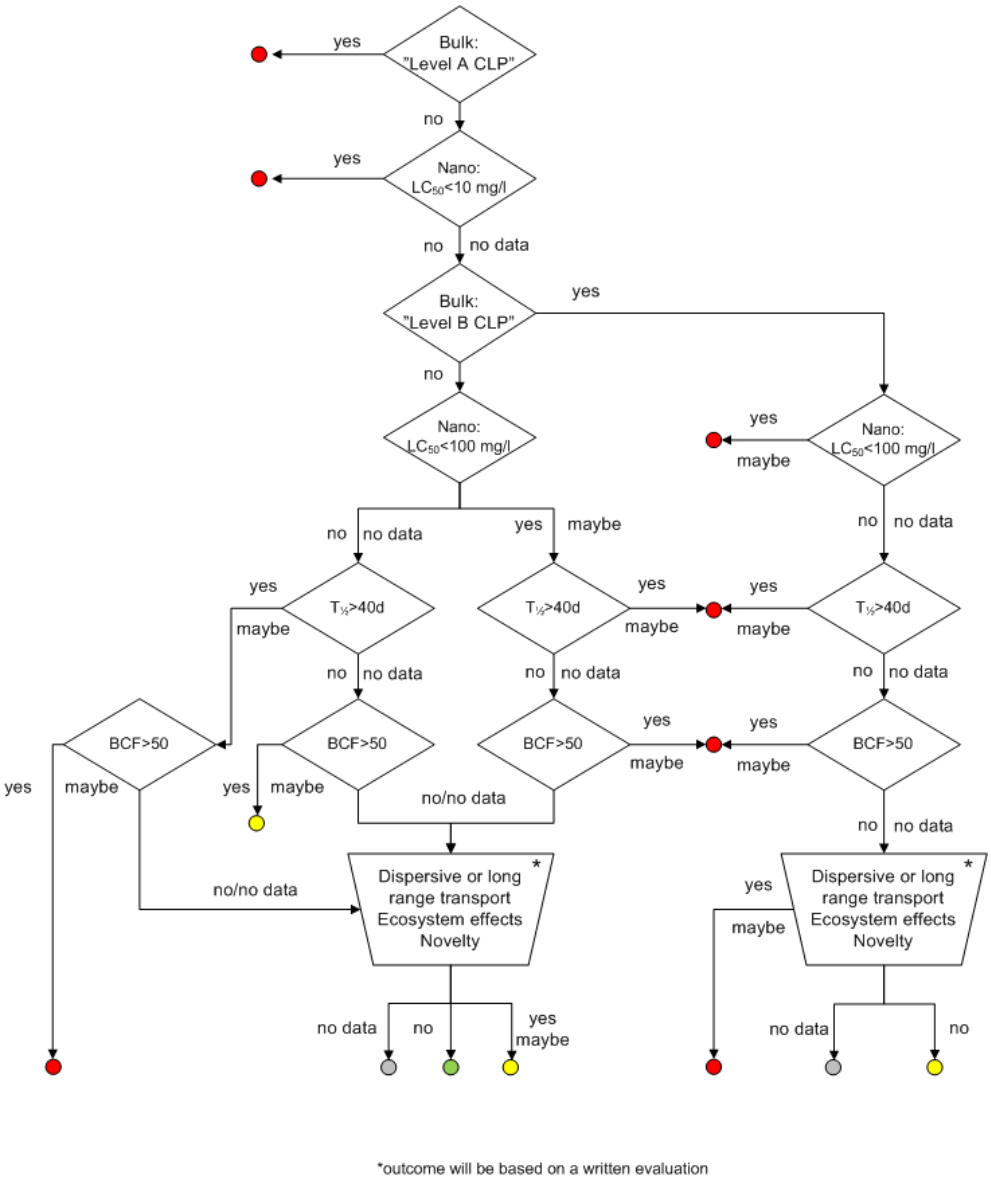

Figure 4. Road-map for assigning an environmental hazard colour code in NanoRiskCat. Red, yellow and green indicate high, medium and low indication of effect whereas grey indicates too limited data to assess effect. For a guide to answering the questions, please refer to sections 3.3.1 to 3.3.9.

It is important to note that NanoRiskCat is a tiered approach in the sense that once a color code has been triggered (e.g. bulk materials CLP classified as Chronic 1 which would trigger "red") the nanomaterial cannot get a different color code (yellow, green or grey) even though the (LC_{50} or EC_{50}) might > 100 mg/l and the half-life might be < 40 days and the BCF < 50.

3.4.1 Bulk – "Level A CLP": Is the bulk form of the nanomaterial classified as CLP Acute 1 or Chronic 1 or Chronic 2?

The first question relates to the hazard characteristics of the bulk or parent version of a nanomaterial and if it is already classified as an Acute 1 or Chronic 1 and Chronic 2. This enables a broad identification of potential hazard (and a form of read-across) from a previously identified hazard associated with the material. In case a nanomaterial does not have a bulk parent material

(e.g. carbon nanotubes and quantum dots) the answer to this question should be no by default.

3.4.2 Nano – LC_{50}<10 mg/l: Is the nanomaterial in question reported to be hazardous to environmental species i.e. LC_{50} or EC_{50} <10 mg/l?

The second question is whether the nanomaterial in question reported to be hazardous to environmental species i.e. LC_{50} or EC_{50} <10 mg/l? Data from the base-set of organisms traditionally used for chemical risk assessment and labelling (i.e. fish, crustacean, and algae) will be given the highest rank. As shown in Figure 4, LC_{50}-values or EC_{50}-values from tests of nanomaterials with base-set organisms below 10 mg/l will lead to a red color coding. Values below 10 mg/l will traditionally be referred to as either toxic (1-10 mg/l) or very toxic (< 1 mg/l) to aquatic organisms. Focus is directed towards well-established endpoints like EC_{50}, NOEC- (No Observed Effect Concentration) and LOEC (Lowest Observed Effect Concentration)-values, but all available ecotoxicity data should be taken into account. The reason for assigning a red color code to materials with LC_{50}- or EC_{50}-values below 10 mg/l is the presently ongoing discussion on which dose-metrics will be the best to use in nano-ecotoxicology. The user of NanoRiskCat should be aware of this rather controversial discussion and may decide to follow a precautionary path, preventing false-positive results (i.e., claiming that a material is not harmful, while in fact it is).

3.4.3 Bulk – "Level B CLP": Is the bulk form of the nanomaterial classified as CLP Chronic 3 or Chronic 4 or documented nano-specifc effects?

The third question relates to whether the bulk material classified as CLP Chronic 3 or Chronic 4 or whether there are documented nano-specific effects. In case the answer is "yes", this rules out the possibility of the nanomaterials in questions being classified as "green". In case a nanomaterial does not have a bulk parent material (e.g. carbon nanotubes and quantum dots) only the questions about documented nanospecific effects have to be addressed. This may apply to cases where statistically significant effects of nanomaterials have been observed, but EC_{50} or LC_{50} values cannot be established or non-standardized endpoints have been applied.

3.4.4 Nano – LC_{50}<100 mg/l: Is the nanomaterial in question reported to be hazardous to environmental species i.e. LC_{50} or EC_{50} <100 mg/l?

This question addresses whether the nanomaterial in question has been reported to be hazardous to environmental species i.e. LC_{50} or EC_{50} <100 mg/l? Data from the base-set of organisms traditionally used for chemical risk assessment and labelling (i.e. fish, crustacean, and algae) will be given the highest rank. As shown in Figure 4, LC_{50}-values or EC_{50}-values from tests of nanomaterials with base-set organisms below 100 mg/l will either lead to a red color coding or a subsequent evaluation of persistency and bioaccumulation potential. The value of 100 mg/l is chosen in accordance to the CLP cut-off values for environmental hazards. Focus is directed towards well-established endpoints like EC_{50}-, NOEC- and LOEC-values, but all available ecotoxicity data should be taken into account.

3.4.5 $T_{½}$>40 days: Is the nanomaterial in question persistent?

The fifth question regards the persistency of the nanomaterial. In NanoRisk-Cat a nanomaterial is considered persistent if freshwater tests reveal a degradation half-life greater than 40 days. If the nanomaterial is carbon-based, tests performed in accordance with the OECD test hierarchy for degradability (OECD 2011) will have the highest rank, but other degradation studies carried out in environmental matrices will also be taken into account in the evaluation. This means that positive results in OECD 301 tests for ready biodegradability (OECD 1992) will result in a "not persistent" categorization. The same goes for positive results of tests for inherent biodegradability (i.e. >70% mineralization) performed in accordance with OECD test guidelines. If <20% mineralization is reached within the incubation period for OECD tests for inherent biodegradability, the materials may be regarded as persistent. In cases where no or insufficient information from OECD tests is available, REACH criteria for persistency will be applied. This means that a material is considered persistent if freshwater tests reveal a degradation half-life greater than 40 days (T½> 40 days in freshwater).

For inorganic nanomaterials the term persistency is not well-defined. On the one hand inorganic nanomaterials can be claimed to be persistent per se since the elements cannot be degraded. In this way all inorganic nanomaterials will be classified as persistent, but attention should be given to the fact that some nanomaterials may be reactive (e.g. nano-scale zero-valent iron that may be oxidized to iron-oxides, or nano-silver that may dissociate to silver-ions) and therefore be transformed to other materials or other forms of the same element. This "new" forms may or may not be nano-scaled. Thus, the recommendation is that non-reactive inorganic nanomaterials are given the classification "persistent" whereas reactive inorganic nanomaterials are classified as "maybe persistent". It is recommended not to use the term "non-persistent" for inorganic nanomaterials.

3.4.6 BCF>50: Is the nanomaterial in question bioaccumulative i.e. BCF>50?

The criterion for classifying a chemical as bioaccumulative according to the REACH guidance is that the bioconcentration exceeds the value of 500. This indicates that the concentration in the organism is 500 times higher than the concentration in the surrounding environment (or that the uptake rate in organisms is 500 times higher than the depuration rate). In NanoRiskCat a cut-off value of 50 is recommended. This value is chosen on a precautionary basis acknowledging that 1) analytical techniques for quantification of nanomaterials in both environmental media and biological tissues are not yet fully developed, and 2) that accumulation of nanomaterials may not be defined by total body burden, but more likely by a differential uptake and perhaps translocation to specific organs. The latter type of behaviour is not comparable to what is known for the dissolved organic chemicals for which the bioconcentration cut-off values originally were defined in the REACH guidance. Nanomaterials will in most cases not be dissolved in the test media, but (at best) be stable suspensions of particles.

Traditionally, an evaluation of the potential for bioaccumulation for organic chemicals is done based on the octanol-water partitioning coefficient (K_{ow}). However, this approach is not considered valid for nanomaterials (Baun ***et al.*** 2009). Therefore, an evaluation of bioaccumulation potential for both organic

and inorganic nanomaterials need to be based on actual measured data either from laboratory or field studies.

3.4.7 Dispersive or long-range transport, ecosystem effects and novelty

As indicated in Figure 4 considerations on the transport, ecosystem effects and novelty should be included as the final step. The outcome of these considerations is a written evaluation aimed at answering "yes", "maybe", "no" or "no data".

The first question to be considered is: Is the nanomaterial dispersive?
Although not something that is normally considered in the environmental hazard categorization, there is historical evidence that the mere fact that a substance or material is disperse in the environment is a good indicator of potential harm that has yet to become discovered (EEA 2001). In relation to this, data on the substance's volatility, solubility and mobility in (e.g. soil) would be of relevance for a "regular" organic chemical, but for nanomaterials, the volatility should be disregarded. The mobility in soil can only be evaluated on actual data measuring the distribution, since no estimation equations have been established for the time being.

The second question to be considered is: Could use of the nanomaterial in question lead to potentially irreversible harm to the environment (e.g. ecosystem effects)?
In the case that a nanomaterial does not fulfil any of the criteria above, a series of broader questions and elements need to be taken in consideration. The first question is whether there are documented or potential ecosystem effects (e.g. through oxygen depletion, effects on nutrient balance, shifts in populations), but also effects on global scale like ozone depletion, or global warming potential.

The final question to be considered is: Are we dealing with a novel material?
Although not something that is normally considered in the environmental hazard categorization, there is historical evidence that the mere fact that a substance or material is novel is a good indicator of potential harm that has yet to become discovered (EEA 2001). No single exhaustive taxonomy exists for novel materials and as noted by Royal Commission on Environmental Pollution (2008) it is unlikely that one is possible or even necessarily desirable. However still, the UK Royal Commission on Environmental Pollution (2008) distinguished between four types of novel materials:

1. new materials hitherto unused or rarely used on an industrial scale;

2. new forms of existing materials with characteristics that differ significantly from familiar or naturally-occurring forms, e.g. silver and gold;

3. new applications for existing materials or existing technological products formulated in a new way, e.g. cerium oxide used as a fuel additive;

4. new pathways and destinations for familiar materials that may enter the environment in forms different from their manufacture and envisaged use (RCEP 2008).

Novel would in this case be defined as materials that humans and environment have not previously been exposed to any significant extent.

3.4.8 Standard sentences associated with environmental hazard classification as red, yellow and grey

To help communicate the scientific reasoning behind assigning an environmental hazard classification and why a given nanomaterial was assigned red, yellow or grey, a number of standard sentences have been developed. Depending on the final classification in regard to environmental hazards, the user of NRC can select one or more of those sentences that best reflect the scientific basis for assigning the color code. A list of these additional sentences is given in Appendix 2, Table A2.2.

4. NanoRiskCat applied in cases

In the following NanoRiskCat is applied on two case studies to serve as examples of how NanoRiskCat could be applied and to assist in the further development of the concept. They involve realistic uses of C_{60} and TiO_2 in products available for professional and non-professional users. While all data are realistic, the product names are constructed. NanoRiskCat is applied to the product by using the guidance provided in Chapter 3 as well as the generic template available in Appendix 1, the additional sentences for explaining color codes in Appendix 2 as well as the defaults colors assigned to various REACH Use Descriptor Categories in Appendix 3.

These two cases illustrate an "expert level" use of NanoRiskCat. This means that a literature review of primary scientific papers form the basis for filling in the NRC template provided in Appendix 1. It is very important that the user uses the NRC template in Appendix 1 for assigning the colors in order to maintain transparency in how the final conclusions were reached.

4.1 Case study 1: C_{60} in lubricant

The following case study is an example of how one could use NanoRiskCat on C60 used in lubricants. The case is based on a realistic use of C60 in a product available for professional and non-professional users. While real data is used, the product name is constructed. NanoRiskCat is applied to this product by filling out the information being asked for in the NRC template available in appendix 1 by using the guidance provided in chapter 3 as well as the series of tables available in Appendix 3 and the additional sentences for explaining color codes in Appendix 2.

NanoRiskCat

Subject: C60 in lubricant "C60 LuBExtreme" produced by Ex-LuB

Nanomaterial description	
Material source or producer:	Carlfullerene Proc.
Manufacturing process:	Arc method
Appearance:	Black powder
Chemical composition:	C60
Physical form/shape:	Powder/spherical
Purity:	99.5%
Size distribution:	~ 1 nm
Solubility:	1.3×10^{-11} mg/mL
State of aggregation or agglomeration:	No information
CAS number (if applicable):	99685-96-8
Product description	
C60 LuBExtreme is a liquid consisting of about 90% base oil and less than 10% additives. Soot-containing C_{60} (up to 1 % in the final product) is mixed together with other chemical additives in order to improve the sliding between metallic surfaces and thereby enhances the performance of the lubricant. The fullerenes molecules work as micro ball-bearings along sliding surfaces.	
Applications	
C60 LuBExtreme is to be used in the form of motor oil to protect the internal combustion engines in motor vehicles and powered equipment. The amount of C60 LuBExtreme needed at each oil shift will depend on the motor engine, but can easily range from 3-6 litres. C60 LuBExtreme is believed to last for minimum 10,000 km and maximum up to 15,000 km. Oil change is recommended after max. 6 months. In order to reduce and to prevent accidents, strict personal and industrial hygiene rules should be respected and contact with the body should be avoided through the use of: oil proof gloves, wearing of clothes with an efficient protection, no wearing of oil contaminated clothes, use of protection cream and no use of solvents, such as petroleum, petrol to remove oil from the skin. Inhalation of oil mists and fumes is possible and efficient ventilation must be installed. The acceptable limit for an oil mist is 1 mg/cm3 (The Danish Working Environment Authority 2002). Wearing goggles is recommended when oil spattering in the eyes are likely to occur.	

Exposure potential for professional end-users

According to table 4 in chapter 3 of the **NanoRiskCat** main report on Criteria for evaluating the exposure profile, the following REACH Use Descriptor Categories are relevant for C60 LuBExtreme.

REACH Cat.	#	Description	**Examples and explanations**
PROC	18	Greasing at high energy conditions	Use as lubricant where significant energy or temperature is applied between the substance and the moving parts
PC	24	Lubricants, greases, release products	
FC		Lubricants and lubricant additives	Substances entrained between two surfaces and thereby used to reduce friction: oils; fats; waxes; friction reducing additives

Exposures to the professional end-user of C60 LuBExtreme are multiple and to be expected. The main risk of direct contact with the C60 LuBExtreme is likely to be skin, eyes, but also airways potentially droplets from splashing and spills. Consequently the skin, eyes, air-ways and GI-tract (through inhalation and hand-to-mouth) are potential exposure routes. The frequency of exposure may be highly depending on profession. Considering the color-codes of the PROC(●), PC (●) and FC (●), we concluded that the overall

Exposure potential for professional end-users is ●

Consumer exposure potential

According to table 4 in chapter 3 of the **NanoRiskCat** main report on Criteria for evaluating the exposure profile, the following REACH Use Descriptor Categories are relevant for C60 LuBExtreme.

REACH Cat.	#	Description	**Examples and explanations**
PC	24	Lubricants, greases, release products	
AC, no intented release		Not applicable	
AC, intented release		Not applicable	

Consumer exposure of C60 LuBExtreme is multiple and to be during filling of oil lubricant. The main risk of direct contact with the C60 LuBExtreme is likely to be skin, eyes, but also airways for fumes and potentially droplets from splashing and spills. Consequently the skin, eyes, air-ways and GI-tract (through inhalation and hand-to-mouth) are potential exposure routes. The frequency of exposure is considered rare. Moreover, the consumer use is presumable by far dominated by oil-filling of relatively low-energy engines.

Considering the color-codes of the PC24 (●) and the non-applicability of AC, we concluded that the overall

Consumer exposure potential is ●

Environmental exposure potential

According to table 4 in chapter 3 of the **NanoRiskCat** main report on Criteria for evaluating the exposure profile, the following REACH Use Descriptor Categories are relevant for C60 LuBExtreme.

REACH Cat.	#	Description	**Examples and explanations**
AC, no intented release		Not applicable	
AC, intented		Not applicable	

release			
ERC	2	Formulation of preparations*	Mixing and blending of substances into (chemical) preparations in all types of formulating industries, such as paints and do-it-yourself products, pigment paste, fuels, household products (cleaning products), lubricants, etc.
ERC	4	Industrial use of processing aids in processes and products, not becoming part of articles	Industrial use of processing aids in continuous processes or batch processes applying dedicated or multi-purpose equipment, either technically controlled or operated by manual interventions. For example, solvents used in chemical reactions or the 'use' of solvents during the application of paints, lubricants in metal working fluids, anti-set off agents in polymer moulding/casting.
ERC	7	Industrial use of substances in closed systems	Industrial use of substances in closed systems. Use in closed equipment, such as the use of liquids in hydraulic systems, cooling liquids in refrigerators and lubricants in engines and dielectric fluids in electric transformers and oil in heat exchangers. No intended contact between functional fluids and products foreseen, and thus low emissions via waste water and waste air to be expected.
ERC	8a	Wide dispersive indoor use of processing aids in open systems	Indoor use of processing aids by the public at large or professional use. Use (usually) results in direct release into the environment/sewage system, for example, detergents in fabric washing, machine wash liquids and lavatory cleaners, automotive and bicycle care products (polishes, lubricants, deicers), solvents in paints and adhesives or fragrances and aerosol propellants in air fresheners.
ERC	8d	Wide dispersive outdoor use of processing aids in open systems	Outdoor use of processing aids by the public at large or professional use. Use (usually) results in direct release into the environment, for example, automotive and bicycle care products (polishes, lubricants, deicers, detergents), solvents in paints and adhesives.

ERC	9b	Wide dispersive outdoor use of substances in closed systems	Outdoor use of substances by the public at large or professional (small scale) use in closed systems. Use in closed equipment, such as the use of hydraulic liquids in automotive suspension, lubricants in motor oil and break fluids in automotive brake systems.

A number of environmental releases of C60 LuBExtreme can be foreseen in the short- and the long-term. C60 might be combusted if oil enters the engine during use or they may be removed together with the oil if they remain suspended in the liquid phase when the oil is changed. Unintended direct release occurring from leaks, spills or sublimation of fullerenes also has to be expected and finally, C60 may adhere to metallic components of the car and will eventually be incorporated in the end-of-life vehicle engine. Environmental exposure during waste handling is possible.

The number of Environmental Release Categories that might be relevant for C60 LuBExtreme is multiple, however a number of the ERCs listed are considered not to be relevant since these are indoor industrial uses and hence fall outside the scope of **NanoRiskCat**. This is the case of ERC 2, 4 and 7.

Considering the color-codes of the ERC 8d (●) and ERC (●) and the non-applicability of AC and ERC 2 (●), ERC4 (●) and ERC7 (●), we concluded that the overall

Environmental exposure potential is ●

Literature methodology/sources of information

Three review articles were primarily used as sources of information to fill out the NanoRiskCat●●●|●● for C60,but where relevant a number of scientific articles were used and cited:

Review articles:

1. Stone V, Hankin S, Aitken R, Aschberger K, Baun A, Christensen F, Fernandes T, Hansen SF, Hartmann NB, Hutchinson G, Johnston H, Micheletti G, Peters S, Ross B, Sokull-Kluettgen B, Stark D, Tran L. 2009. Engineered Nanoparticles: Review of Health and Environmental Safety (ENRHES). Available: http://nmi.jrc.ec.europa.eu/project/ENRHES.htm (Accessed July 15, 2010)
2. Shinohara, N., Nakamishi, J., Gamo, M. 2009. Risk Assessment of Manufactured Nanomaterials – C60. Available: http://www.aist-riss.jp/main/modules/product/nano_rad.html?ml_lang=en (Accessed July 15, 2010)
3. Nielsen GD, Roursgaard M, Jensen KA, Poulsen, SS, Larsen ST. In vivo biology and toxicology of fullerenes and their derivatives. Basic Clin Pharmacol Toxicol 2008;103(3):197-208

Human hazard profile

1. **Does the nanomaterial fulfil the HARN paradigm?**

   Answer: No
   Argument and explanation: The primary C60 molecule has the shape of a soccer ball and has a diameter of less than 1 nm. At concentrations above the solubilisation limit C60 spontaneously form aggregates or so-called fullerene crystals of 25-500 nm in various suspension including water, ethanol and acetone (Shinohara *et al.* 2009)

2. **Is the bulk form of the nanomaterial known to cause or may cause serious damaging effects, i.e. is the bulk form classified according to the CLP with regard to one or more serious health hazards such as germ cell mutagenicity, carcinogenicity or reproductive toxicity in category 1A, 1B or 2?**

   Answer: Not relevant
   Argument and explanation: No bulk form of C60 exists

3. **Is the bulk form of the nanomaterial classified for other less severe adverse effects according to the CLP such as skin corrosion/irritation category 2 and specific target organ toxicity-single exposure category 3?**

   Answer: Not relevant
   Argument and explanation: No bulk form of C60 exists

4. **Is the specific nanomaterial known to be acute toxic?**

   Answer: No
   Argument and explanation: According to Stone *et al.* (2009):
   "…different fullerene types have been shown in two studies to have a very low toxicity after oral exposure as no signs of toxicity have been described for the doses tested. From the identified data it might be possible to derive a NOAEL of 2000 mg kg-1 bw for fullerite (mixture of C60 and C70) (Mori et al. 2006) and of 50 mg kg-1 for polyalkylsufonated (water soluble) C60 (Chen et al. 1998b). As only one dose was tested and no dose with an effect has been determined (reported) it might be possible that a higher NOAEL could be determined, especially for the polyalkylsulfonated C60."…

   "*Following pulmonary exposure fullerenes have shown no or low ability to induce inflammation or even anti-inflammatory responses.*"…

   "*The only identified study investigating effects following dermal exposure (human patch test with fullerene soot) found no detrimental outcome.*"

   "*Following intraperitoneal injection kidney, liver and spleen have been demonstrated to be a target of fullerene toxicity. An LD_{50} of 600 mg kg-1 was determined. Mice have shown to be able to generate antibodies against the C60 derivatives, which were also active against other nanoparticles (SWCNT). The relevance of the findings following intraperitoneal injection for primary routes of exposure (inhalation, dermal and oral) has to be further examined in light of the questionable uptake via these routes.*" (Stone *et al.* 2009).

5. Are there indications that the nanomaterial causes genotoxic, mutagenic, carcinogenic, respiratory, cardiovascular neurotoxic or reproductive effects in humans and/or laboratory animals or has organ-specific accumulation been documented?

   Answer: Maybe
   Argument and explanation:

a. Genotoxicity and mutagenicity: A number of genotoxicity test have been reported on in the scientific literature. For a recent review, see Stone *et al.* (2009). Studies on C60 suspended in solvents were considered irrelevant for C60 LuBExtreme and so was studies reported on fullerol. A couple of studies has found evidence of genotoxicity of C60. Dhawan *et al.* (2006) investigated whether C60 was able to inflict DNA damage within human lymphocytes, and was detected using the Comet assay, when exposed at concentrations ranging from 0.42 to 2100 μg l-1, for up to 6 hours. Sera *et al.* (1996) investigated the mutagenic effect of fullerene exposure (up to 30 μg per plate, for 48 hours) on Salmonella typhimurium, in light and dark conditions using the Ames test. If exposure occurred within the dark, no mutagenic responses were evident. In contrast, a mutagenic effect was observed, when exposure occurred in the presence of visible light, due to the production of ROS, which interact with DNA to elicit damage, and was typified by the formation of 8-hydroxydeoxyguanosine. Lipid peroxidation was also increased by fullerene exposure in light, further highlighting the oxidative consequences associated with light irradiation. Stone *et al.* (2009) concludes: "Genotoxicity has not been associated with fullerene exposure in a number of studies. Mori *et al.* (2006) investigated the mutagenicity of a C60/C70 mixture. It was illustrated that no mutagenic responses were evident within a variety of Salmonella typhimurium and Escherichia Coli strains, using the Ames test (up to 5000 μg per plate). In addition, within the chromosomal aberration test (in CHL/IU hamster lung cells) no aberrations within the structure or number of chromosomes were apparent. Furthermore, Jacobsen *et al.* (2008) investigated the mutagenicity associated with a number of carbon based nanoparticles, including C60 within the mouse FE1-Muta epithelial cell line. It was demonstrated that C60 exposure (0-200 μg ml-1, 24 or 576 hours) was associated with a slight increase in ROS production in cells and in cell free conditions, but no impact on cell viability was observed. C60 was not capable of eliciting strand breaks, and no alterations in mutation frequency were observed when using the Comet assay." Thus, according to Stone *et al.* (2009) the evidence of genotoxicity of C60 is contradictory and therefore difficult to interpret from the studies conducted so far.

b. Respiratory tract toxicity: Following pulmonary exposure fullerenes have shown no or low ability to induce inflammation or even anti-inflammatory responses according to Nielsen *et al.* 2008 and Stone *et al.* (2009). Sayes *et al.* (2007a), however, did observe an increase in the percentages/numbers of Bronchoalveolar lavage (BAL)-recovered neutrophils (i.e. white blood cells) after intratracheally instillation of C60 and hydroxylated C60 i.e. C60(OH)24 just 1 day post-exposure. Sayes *et al.* (2007a) also observed a significant increase in lipid peroxidation values and an increase in level of glutathione (GSH), after 1 week. Lai *et al.* (2000) also observed a significant increase in lipid peroxidation products after intravenous administration of 1 mg C60(OH)18 per kg into male mongrel dogs previously induced with infusion/reperfusion injury. In contrast to Sayes *et al.* (2007a), Lai *et al.* (2000) observed a decrease in the GSH level in intestinal tissue. Adelman *et al.* (1994) observed a reduction of the viability of bovine alveolar macrophages compared to control after exposure to sonicated C60 along with increased levels of cytokine mediators of inflammation (i.e. TNF, IL-6 and IL-8) whereas Baierl *et al.* (1996) and Porter *et al.* (2006) found that C60 and raw soot was not toxic towards bovine- and human alveolar macrophages. The alveolar macrophage serves as the first line of cellular defense against respiratory pathogens (Rubins 2003) and hence studies reporting on the effects on alveolar macrophages are of special interests.

c. Cardiovascular toxicity: To the best of our knowledge no epidemiological or animal study has been reported on in the scientific literature investigated the effects of C60 on the cardio-vascular system.

d. Neurotoxicity: To the best of our knowledge no epidemiological or animal study has been reported on in the scientific literature investigated the neutotoxic potential of C60.

e. Reproductive damage: Stone *et al.* (2009) recently reviewed the reproductive toxicology of fullerenes. Three studies were reviewed, however only one of them are considered directly relevant for C60 LuBExtreme. In one study C60 had been solubilised in polyvinylpyrrolidone and administered intraperitoneally to pregnant mice (Tsuchiya *et al.* 1996) and in another THF suspended C60 was used to study the cytotoxicity of C60 in Chinese hamster ovary mammalian cell line (Han and Karim 2009). PVP and THF is not used in the production of C60 LuBExtreme and hence these studies were found to be only partially relevant. Collectively, these results, illustrate the potential toxicity of fullerene particles in mammalian ovary cells (Stone *et al.* 2009). However studies are extremely limited in number and in sample size. Only one study identified examined effects on an

ovarian cell line model with no studies focused on other organs or cell types in the female reproductive system. No specific in vitro or in vivo studies were found examining fullerene effects in male reproductive system.

f. Carcinogenicity: To the best of our knowledge no epidemiological or animal study has been reported on in the scientific literature investigated the carcinogenic potential of C60.

g. Does the nanomaterials accumulate in tissue and/or organs?: According to Stone *et al.* (2009) *"Information regarding the ADME profile of fullerenes is generally lacking, and therefore warrants further investigation in future studies. In the small number of studies described here, it would appear that the majority of fullerenes remain at the deposition site (specifically within the lungs and gut), but that it is also possible for fullerenes to cross cell barriers and to be transported within the blood. Accumulation appears to be predominant within the liver, kidneys and spleen, with evidence of toxicity also manifesting at sites of accumulation. Metabolism of fullerenes has also been suggested, and the consequences of this require consideration. Elimination of fullerenes within the faeces and urine has also been demonstrated, which may reduce their propensity for distribution and toxicity. However, it is relevant to note that the representative nature of the limited number of findings, for all fullerene derivatives is unknown at this time."*

Stone *et al.* (2009) furthermore state that: *"The findings from the different studies therefore share the commonality, that subsequent to injection, fullerenes preferentially accumulate within the liver. Therefore it is of high relevance to evaluate the impact of fullerene accumulation on liver function, and to assess the contribution of the liver to the metabolism of fullerenes and, in addition to considering the ability of the liver to facilitate the removal of fullerenes from the body within bile, and therefore the faeces."*

The overall answer to this question is "Maybe" based on the following considerations:

1. Mutagenic effect have been observed, when exposure occurred in the presence of visible light, due to the production of ROS, which interact with DNA to elicit damage whereas the evidence of genotoxicity of C60 is contradictory and therefore difficult to interpret from the studies conducted so far.

2. In regard to respiratory damage an increase in the percentages/numbers of Bronchoalveolar lavage (BAL)-recovered neutrophils (i.e. white blood cells) after intratracheally instillation has been reported and so has a reduction of the viability of bovine alveolar macrophages

3. Based on studies found only to be partially relevant for C60 LubExtreme data of reproductive damage collectively illustrate the potential toxicity of fullerene particles in mammalian ovary cells.

4. To the best of our knowledge no epidemiological or animal study has been reported on in the scientific literature investigated the carcinogenic-, cardio-vascular and neurotoxic potential of C60.

5. Though indications of accumulation of fullerenes in organs have been described the very few findings that exist at this point in time rather call for the answer "maybe" than the answer "yes"

6. Overall evaluation of human hazard

Based on a holistic evaluation of the evidence summarized above and sub-conclusion reached, we concluded that the color-code that best reflects the human hazard profile of C60 in C60 LuBExtreme is • based on in vitro evidence indicating at least one nanospecific hazard.

Environment hazard profile

1. **Bulk material classified as CLP Acute 1 or Chonic 1 or Chronic 2?**

   Answer: No
   Arguments and explanation: C60 does not have a meaningful bulk parent materials and hence the answer to this question is no by default.

2. **Is the nanomaterial in question reported to be hazardous to environmental species i.e. LC_{50} or EC_{50} <10 mg/l?**

   Answer: Yes
   Arguments and explanation: According to Stone *et al.* (2009) "*The information available so far leads to the conclusion that non-functionalised C_{60} is toxic for aquatic organisms. A study with fish observed sub-lethal effects on growth at 0.04 mg l^{-1}*".
   In the short-term studies with crustaceans lethal concentrations were 7.9 mg l^{-1} (LC_{50}) for D. magna exposed to sonicated C60 and over 22.5 mg l^{-1} for copepod species exposed to stirred C60. Long-term exposure of Daphnia magna to 2.5 mg l^{-1} C60 revealed in a delay of moulting and a significant reduction in offspring. However, the effect on reproduction could have been caused by mortality which occurred from day 5 onwards. A $NOEC_{Daphnia}$ (long-term) should be < 2.5 mg l^{-1} C60 (Stone *et al.* 2009). Hence non-functionalized C60 has been reported to be hazardous to environmental species i.e. LC_{50} or EC_{50} <10 mg/l and this indicator is fulfilled which leads to the color code of "red"

3. Overall evaluation of environmental hazard

We concluded that the color-code that best reflects the environmental hazard profile of C60 used in C60 LuBExtreme is • **based on nanospecific LC_{50} or EC_{50} < 10 mg/l.**

Summary

This information provided and summarized in this template is considered to be accurate at the date of printing and is believed to be a complete reflection of what the Ex-Lub knows about the risks of using C60 as an additive to enhance the performance of C60 LuBExtreme.

Exposure			Effects	
Prof	**Consum**	**Environ**	**Human**	**Environ**
●	●	●	●	●
			7b[a)]	2[b)]

Red, yellow and green indicate high, medium and low indication of exposure/effect level whereas grey indicates too limited data to assess exposure/effect; a) "based on in vivo evidence of a combination of hazards from testing of the nanomaterial" (see Appendix 2, Table A2.1); b) "based on LC_{50} or EC_{50} < 10 mg/l for the testing of the nanomaterial" (see Appendix 2, Table A2.2)

The overall **NanoRiskCat** code for the C60 in C60 LubExtreme is ●●●|●●

NanoRiskCat does not lead directly to a decision, but provides a basis for decision-making by defining a number of concrete criteria that defines to which extend there are indication of exposures and effects for professional users, consumers, and the environment.

It is the reader's obligation to evaluate this NRC in the light of any new scientific evidence regarding risks published after the data of printing and to comply with all applicable laws and regulations.

Date of printing **Signature**

……/……/…… ……..

4.2 Case study 2: TiO_2 in sunscreen

The following case study is an example of how one could use NanoRiskCat on TiO_2 used in sunscreen. The case is based on a realistic use of TiO_2 in a product available for professional and non-professional users. While real data from litterature is used, the product name is constructed. NanoRiskCat is applied to this product filling out the information being asked for in the NRC template available in appendix 1 by using the guidance provided in Chapter 3 as well as the series of tables available in Appendix 1 and the additional sentences for explaining color codes in Appendix 2.

NanoRiskCat

Subject: TiO_2 **in SunPro SPF 50 by SunProMax**

Nanomaterial description	
Material source or producer:	TiO_2 Ltd (SunProMax is not primary producer of TiO_2)
Manufacturing process:	Flame hydrolysis
Appearance:	White powder
Chemical composition:	TiO_2, uncoated
Physical form/shape:	Powder/spherical
Purity:	> 95% rutile
Size distribution:	20-25 nm
Solubility:	Insoluble (H_2O)
State of aggregation or agglomeration:	70-90 nm aggregates/agglomerates
CAS number (if applicable):	1317-80-2

Product description

SunPro SPF entails 15% 20-25 nm nanoTiO_2. NanoTiO_2 is used as a sunfilter that protects against UVB as well as UVA. SunPro SPF 50 reduction of UVA and UVB is 90% and 96%, respectively. SunPro SPF 50 does not penetrate the skin, but acts as a protecting white layer on the skin that reflects the sunrays. This type of filters is called physical filters and is well suited for the both kids and adults.

Applications

It is important to use plenty of sunscreen, 30-40 ml, in order to achieve the optimal effect. In order to achieve the optimal protection the sunscreen should be applied before sunbathing is initiated and repeated depending on the need. Never let infants stay directly exposed to the sun. Always protect children against intense sunrays by making them wear hat and appropriate clothes. Furthermore, avoid exposure to the sun in the middle of the day, i.e. 12-15 pm, when the sunrays are the most intensive.

Exposure potential for professional end-users

According to table 4 in chapter 3 of the **NanoRiskCat** main report on Criteria for evaluating the exposure profile, the following REACH Use Descriptor Categories are relevant for SunPro SPF 50.

REACH Cat.	#	Description	**Examples and explanations**
PROC	Not applicable		
PC	39	Cosmetics, personal care products	

FC	Not applicable		

Exposures to the professional end-users of SunPro SPF50 are multiple and to be expected. As full body skin exposure is recommended when exposed to sunrays, and although minor levels of ingestion is to be expected, inhalation can be ruled out.

No PROC or FC was found to be relevant for the use of TiO_2 in SunPro SPF50.

Considering the color-codes of PC34 (●), we concluded that the overall

Exposure potential for professional end-users is ●

Consumer exposure potential

According to table 4 in chapter 3 of the **NanoRiskCat** main report on Criteria for evaluating the exposure profile, the following REACH Use Descriptor Categories are relevant for SunPro SPF 50.

REACH Cat.	#	Description	**Examples and explanations**
PC	39	Cosmetics, personal care products	
AC, no intented release	Not applicable		
AC, intented release	Not applicable	<<Insert description of this AC, intended release >>	

Consumer exposure to SunPro SPF 50 are multiple and to be expected. As full body skin exposure is recommended when exposed to sunrays, and although minor levels of ingestion is to be expected, inhalation can be ruled out.

No AC, no intended release or AC, intended release was found to be relevant for the use of TiO_2 in SunPro SPF50.

Considering the color-codes of the PC39 (●), we concluded that the overall

Consumer exposure potential is ●

Environmental exposure potential

According to table 4 in chapter 3 of the **NanoRiskCat** main report on Criteria for evaluating the exposure profile, the following REACH Use Descriptor Categories are relevant for SunPro SPF 50.

REACH Cat.	#	Description	**Examples and explanations**
AC, no intended release	<<Insert number of first relevant AC, no intended release >>	<<Insert description for this AC, no intended release >>	<<Insert examples and explanations for this AC, no intended release >>
AC, intended release	Not applicable		
ERC	8a	Wide dispersive indoor use of processing aids in open systems	Indoor use of processing aids by the public at large or professional use. Use (usually) results in direct release into the environment/sewage system, for example, detergents in fabric washing, machine wash liquids and lavatory cleaners, automo-

			tive and bicycle care products (polishes, lubricants, deicers), solvents in paints and adhesives or fragrances and aerosol propellants in air fresheners.
ERC	8d	Wide dispersive outdoor use of processing aids in open systems	Outdoor use of processing aids by the public at large or professional use. Use (usually) results in direct release into the environment, for example, automotive and bicycle care products (polishes, lubricants, deicers, detergents), solvents in paints and adhesives.

Environmental exposure to SunPro SPF 50 are multiple and to be expected.

The main outlets to the environment are expected to be directly into the water recipients and/or indirectly via the STPs into water recipient and soil.

Considering the color-codes of the ERC 8a(•) and ERC 8d(•), we concluded that the overall

Environmental exposure potential is ●

Literature methodology/sources of information

Two sources of information were used to fill out the NanoRiskCat for TiO_2:

1. Stone V, Hankin S, Aitken R, Aschberger K, Baun A, Christensen F, Fernandes T, Hansen SF, Hartmann NB, Hutchinson G, Johnston H, Micheletti G, Peters S, Ross B, Sokull-Kluettgen B, Stark D, Tran L. 2009. Engineered Nanoparticles: Review of Health and Environmental Safety (ENRHES). Available at: http://nmi.jrc.ec.europa.eu/project/ENRHES.htm (Accessed July 15, 2010)
2. Shinohara, N., Nakamishi, J., Gamo, M. 2009. Risk Assessment of Manufactured Nanomaterials – TiO_2. (Available: http://www.aist-riss.jp/main/modules/product/nano_rad.html?ml_lang=en (Accessed July 15, 2010)

Human hazard profile

1. **Does the nanomaterial fulfil the HARN paradigm?**

   Answer: No
   Arguments and explanation: Nanoparticles used in SunPro SPF 50 by SunProMax are 20-25 nanometer and spherical

2. **Is the bulk form of the nanomaterial known to cause or may cause serious damaging effects, i.e. is the bulk form classified according to the CLP with regard to one or more serious health hazards such as germ cell mutagenicity, carcinogenicity or reproductive toxicity in category 1A, 1B or 2?**

   Answer: No
   Arguments and explanation: To the best of our knowledge TiO_2 has no CLP classifications

3. **Is the bulk form of the nanomaterial classified for other less severe adverse effects according to the CLP such as skin corrosion/irritation category 2 and specific target organ toxicity-single exposure category 3?**

   Answer: No
   Arguments and explanation: To the best of our knowledge TiO_2 has no CLP classifications

4. **Is the specific nanomaterial nanoform of the materials known to be acute toxic?**

Answer: No
Arguments and explanation: According to Stone *et al.* (2009) no in vivo studies have been identified in regard oral and dermal acute toxicity. In regard to inhalation toxicity, several authors have shown that TiO_2 nanoparticles (with a size in the range of about 20-30 nm) is considerably more toxic than its micro- TiO_2 (> 100nm) counterpart (see e.g. Ferin *et al.* 1992; Renwick *et al.* 2004; Chen *et al.* 2006; Inooue *et al.* 2008). After having exposed 2 times 10 mice to nanoTiO_2 via intraperitional injection, Chen *et al.* (2006) reported observing that a total of five mice died after exposure to 1944 and 2592 mg/kg, respectively. From this can be derived that the acute toxicity estimates are > 5 mg/l.

5. Are there indications that the nanomaterial causes genotoxic, mutagenic, carcinogenic, respiratory, cardiovascular neurotoxic or reproductive effects in humans and/or laboratory animals or has organ-specific accumulation been documented?

Answer: Yes
Arguments and explanation:

a. Genotoxicity and mutagenicity: According to Stone *et al.* (2009) "TiO_2 *nanoparticles are not expected to cause direct mutagenicity/genotoxicity (although further testing may be needed to fully confirm this), but may trigger genotoxicity via an indirect threshold driven mechanism involving oxidative stress.*"

b. Respiratory tract toxicity: According to Stone *et al.* (2009) several authors have shown that TiO_2 nanoparticles (with a size in the range of about 20-30 nm) is considerably more toxic than its micro- TiO_2 (> 100nm) counterpart (see e.g. Ferin *et al.* 1992; Renwick *et al.* 2004; Chen *et al.* 2006; Inooue *et al.* 2008). Most studies identified used a single dose of particles, administered via intratracheal instillation and toxicity observed included: pulmonary inflammatory response (characterised by neutrophil and macrophage infiltration) (Ferin *et al.* 1992; Chen *et al.* 2006; Warheit *et al.* 2007; Inoue *et al.* 2008; Renwick *et al.* 2004; Grassian *et al.* 2007); epithelial damage, increased permeability of the lung epithelium, and cytotoxicity, which were measured within the bronchoalveolar lavage fluid (BALF) (Renwick *et al.* 2004); and morphological alteration within the lung (Chen *et al.* 2006). Finally, Ahn *et al.* (2005) using a high dose (4 mg kg^{-1}) investigated what processes were responsible for particulate mediated stimulation of excessive mucus secretion within humans. TiO_2 exposure stimulated an increase in goblet cell hyperplasia, which is, in part, attributed to an increase in muc5 gene expression and IL-13 production. Therefore, it could be speculated that particle mediated increases in mucus secretion contributed to the aggravation of chronic airway disease symptoms within humans, and therefore warrants further investigation. Grassian *et al.* (2007) investigated the toxicity of TiO_2 nanoparticles (5 and 21 nm) within mice, subsequent to inhalation (0.7 or 7 mg m^{-3}, for 4 hours) or nasal instillation (up to 150 µg per 50 µl). An elevated macrophage population was associated with the inhalation of particles (4 and 24 hours post exposure), and were observed to internalise particles. An infiltration of neutrophils was associated with the nasal instillation of TiO_2. Several authors suggested that the response subsequent to TiO_2 exposure was dose driven (e.g. Chen *et al.* 2006; Renwick *et al.* 2004). In the Renwick *et al.* (2004) study, no toxicity was seen at 125 µg per rat (corresponding to 0.5 µg kg^{-1} assuming a rat weight of 250 g), whereas toxicity was seen at the high dose of 500 µg per rat (particle size 29nm). Chen *et al.* (2006) exposed mice and found toxicity (inflammation and histological changes in the lung) at the lowest dose of 100 µg per mouse (corresponding to 33 µg kg^{-1} assuming a mouse weight of 30 g) (particle size 19-21 nm). Although the Chen *et al.* (2006) study does not indicate a no effect level, it seems justified (assuming the rat is more sensitive) to estimate, a No Observed Adverse Effect Level (NOAEL) of 125 µg per rat (corresponding to 0.5 µg kg^{-1}). The crystallinity of TiO_2 nanoparticles is thought to influence the toxicity with the anatase form expected to be more toxic that the rutile form (Warheit *et al.* 2007).

c. Cardio-vascular toxicity: According to Stone *et al.* (2009) "*Helfenstein et al. (2008) showed that* TiO_2 *nanoparticles were able to affect cardiomyocyte electrophysiology, enhance ROS production, and reduce myofibril organisation, whereas Peters et al. (2004) found* TiO_2 *relatively low-toxic to HDMEC endothelial microvascular cells (with minimal IL-8 release).*"

d. Neurotoxicity: Long *et al.* (2006, 2007) indicates that TiO_2 nanoparticles caused a ROS driven toxicity to some types of cells of the CNS in vitro. According to Stone *et al.* (2009) *"Wang et al. (2008a) investigated the distribution of rutile (80 nm) and anatase (155 nm) TiO_2 particles within the mouse brain, following nasal instillation exposure (500 µg per mouse, every other day for a total of 30 days) and determined if any neurotoxicity associated with exposure. Both forms of TiO_2 were able to access the brain, with accumulation within the cerebral cortex, thalamus and hippocampus evident, and was postulated to occur via the olfactory bulb. This route of uptake however, was unlikely to be mediated via penetration into the cardiovascular system and via the blood. Instead, TiO_2 delivery to the brain occurred via neuronal transport, with preferential localisation evident within the hippocampus and olfactory bulb. Accumulation of TiO_2 resulted in morphological alterations and loss of neurones in the hippocampus, which was accounted for by the higher distribution of TiO_2 within this brain region. In addition it was suggested that TiO_2 elicited oxidative stress within the brain due to the elevation of superoxide dismutase (SOD), and catalase activity, and evidence of increased lipid peroxidation and protein oxidation. Therefore neuronal mediated translocation of TiO_2 to the brain, following nasal instillation, was observed, with the hippocampus illustrated as being the main target of accumulation and toxicity. Wang et al. (2008b) expanded upon these findings and found that the phenomenon was time dependent (was maximal at 30 days), and that an inflammatory response (indicated by IL-1β, and TNFα) within the brain was also stimulated by TiO_2 exposure. The response was measured at day 2, 10, 20, and 30. It was apparent that repeated exposures, over a period of 30 days, were required to enable the accumulation of TiO_2 within the brain. It is therefore of interest that the neuronal transport of nanoparticle containing substances between the nose and CNS could be exploited, in order to bypass the blood brain barrier".*

e. Reproductive damage: Komatsu *et al.* (2008) has shown that TiO_2 nanoparticles are taken up by and affect viability, proliferation and gene expression of Leydig cells (testosterone producing cells of the testis) in vitro, whereas one in vitro study suggests that TiO_2 nanoparticles may be toxic towards Leydig cells. However, given the toxico-kinetics, it can be questioned whether TiO_2 can indeed reach these cells. No studies investigating female fertility were identified. Overall, no conclusion can be drawn (Stone *et al.* 2009). No information has been identified on developmental toxicity and hence and no conclusion can be drawn.

f. Carcinogenicity: One study has described finding tumour following chronic inhalation after repeated exposure (Heinrich *et al.* 1995). The study used very high doses and had a long duration (high death in the control group). NIOSH (2005) concluded, based on those data that TiO_2 is carcinogenic in rats and that it cannot be excluded to be carcinogenic in humans. It is expected that carcinogenicity occurs following pulmonary overload and thus has a threshold (Stone *et al.* 2009). It should be noted that also the International Agency for Research on Cancer have assessed TiO_2 (even the microform – if exposure is high enough) to be a Class 2B carcinogen (Possibly carcinogenic to humans) (IARC 2006).

g. Does the nanomaterials accumulate in tissue and/or organs?: As noted by Stone *et al.* (2009) there is limited evidence in regard to whether TiO_2 accumulate in tissue and/or organs. According to Stone *et al.* (2009) *"Fabian et al. (2008) determined the tissue distribution of TiO_2 nanoparticles (20-30 nm) within rats, at 1, 14 and 28 days post exposure, via intravenous injection (5 mg kg-1). TiO_2 was cleared from the blood and primarily accumulated within the liver, but was also apparent within the spleen, lungs and kidneys. The level of TiO_2 was retained over the observation time within the liver, however levels decreased with time within the other organs. No serum cytokine or enzyme changes, which insinuated that no toxicity was associated with TiO_2 exposure, however further investigations, including histopathological analysis would be necessary to confirm this. Wang et al. (2008a) investigated the distribution of rutile (80 nm) and anatase (155 nm) TiO_2 particles within the mouse brain, following nasal instillation exposure (500 µg per mouse, every other day for a total of 30 days) and determined if any neurotoxicity associated with exposure. Both forms of TiO_2 were able to access the brain, with accumulation within the cerebral cortex, thalamus and hippocampus evident, and was postulated to occur via the olfactory bulb."*

6. Overall evaluation of human hazard

The overall answer to this question is "Yes" based on the following considerations:

1. The widely reported respiratory damage caused by nanoTiO_2

2. NanoTiO_2 has been associated with carcinogenic-, cardiovascular and neurotoxic and reproductive damage

We conclude that the color-code that best reflects the human hazard profile of TiO_2 used in SunPro SPF50 is ● based on in vivo evidence indicating at least one nanospecific hazard

Environment hazard profile

1. **Bulk material classified as CLP Acute 1 or Chronic 1 or Chronic 2?**

   Answer: No
   Arguments and explanation: Bulk TiO_2 has to the best of our knowledge not be classified a CLP Acute 1 or Chronic 1 or 2

2. **Is the nanomaterial in question reported to be hazardous to environmental species i.e. LC_{50} or EC_{50} <10 mg/l?**
   Answer: Yes
   Arguments and explanation: Following U.S. Environmental Protection Agency (2002) standard protocol, Zhu *et al.* (2008) reported deriving an $LC_{50,72h}$ of 2.02 mgl-1 for nano- TiO_2 on the crustacean Daphnia magna.

3. **Overall evaluation of environmental hazard**

   The overall answer to this question is "Yes" based on the fact that nano- TiO_2 has been reported to be hazardous to environmental species i.e. LC_{50} or EC_{50} <100 mg/l and this indicator is fulfilled which leads to the color code of "red"

We concluded that the color-code that best reflects the environmental hazard profile of TiO_2 used in SunPro SPF50 is ● based on nanospecific LC_{50} or EC_{50} < 10 mg/l

Summary

This information provided and summarized in this template is considered to be accurate at the date of printing and is believed to be a complete reflection of what the SunProMax knows about the risks of using TiO_2 as an UV filter to reflect UVA and UVB sunrays in SunPro SPF50.

Exposure			Effects	
Prof	**Consum**	**Environ**	**Human**	**Environ**
●	●	●	●	●
			8b[a)]	2[b)]

Red, yellow and green indicate high, medium and low indication of exposure/effect level whereas grey indicates too limited data to assess exposure/effect; a) "based on in vitro evidence of a combination of hazards from testing of the nanomaterial" (see Appendix 2, Table A2.1); b) "based on LC_{50} or EC_{50} < 10 mg/l for the testing of the nanomaterial" (see Appendix 2, Table A2.2)

The overall **NanoRiskCat** code for the use of TiO_2 in SunPro SPF50 is: ●●●|●●

NanoRiskCat does not lead directly to a decision, but provides a basis for decision-making by defining a number of concrete criteria that defines to which extend there are indication of exposures and effects for professional users, consumers, and the environment

It is the reader's obligation to evaluate this NRC in the light of any new scientific evidence regarding risks published after the data of printing and to comply with all applicable laws and regulations.

Date of printing **Signature**

……/……/…… **……..**

5. Use(s) of NanoRiskCat

In previous chapters of this report the structure of the decision-support tool NanoRiskCat has been described. The development of NanoRiskCat was initiated after a need had been identified for the development of a new concept to provide support to companies and regulators in regard to identifying, ranking and communicating their knowledge of the risks of nanomaterials in specific uses in products.

5.1 Communication of the results of NanoRiskCat

In its simplest form the final outcome of using NanoRiskCat for a nanomaterial in a given application will be communicated in the form of a short title describing the use of the nanomaterial and five color-coded dots (e.g. •••| ••). The red, yellow and green colored dots respectively indicate high, medium and low indication of exposure or effect whereas the grey indicates that the data available is too limited to assess the possibility for exposure or effect. It's important to underline that the color refers to a high/medium/low ***indication*** of exposure/hazard and does not in itself give a ***definitive*** categorization.

NanoRiskCat is focussed on evaluating the nanomaterial as an ingredient under the physical conditions it occurs under in the product. Hence, NanoRiskCat does not evaluate exposure and effects from the other constituents and impurities in the product nor does it take into account the specific content of nanomaterial in the product. Thus, NanoRiskCat is directed towards the generic use descriptors and scenarios, which for instance are apparent in the product categories used in REACH. It is the hope the NanoRiskCat will contribute to the safe handling nanomaterials in specific applications and it is important to underline that filling out NanoRiskCat cannot be used to pass judgment about the safety of other applications of a given nanomaterial.

NanoRiskCat can primarily be used to understand and categorize what is known about the hazard and exposure of using a given nanomaterial in a given application. By following the sketched format provided in NanoRiskCat and by filling out the NRC template provided in Appendix 1, users will be able to sort, systematize and structure human and environmental hazard information on nanomaterials into an easily understandable and communicable format. The final outcome of NanoRiskCat (the short title of use scenario, the color coding and standard sentences) will make it clear whether it is the professional end-users, consumers and/or the environment that is primarily exposed and whether there are high, medium and low indications of human and environmental effects. NanoRiskCat may also inform users of what kind of information is currently not available. For instance, it might be an element of concern if there is a high indication of environmental exposure, but not data available on the environmental hazards of the nanomaterial.

5.2 Pros and cons of NanoRiskCat

The NanoRiskCat code of C_{60} in lubricant was •••|•• based on ***in vitro*** evidence indicating at least one nanospecific human hazard and nanomaterial

specific LC_{50} or EC_{50} values below 10 mg/l indicating environmental hazard. For TiO_2 in sunscreen the NanoRiskCat code was ●●●|●● based on ***in vivo*** evidence indicating at least one nanospecific human hazard being associated with nanoTiO2 and a nanomaterial specific LC_{50} or EC_{50} < 10 mg/l for daphnids indicating environmental hazard.

When interpreting these color codes, it is important to be aware of the strengths and weaknesses of NanoRiskCat. A significant strength of NanoRiskCat is that it can be used even in cases where lack of data is prominent and hampers the completion of traditional risk assessment procedures. Another is that the results of NanoRiskCat can be easily communicated with other interested parties. A significant weakness of NanoRiskCat is that many of the cut-off values used primarily in the environmental hazard evaluation are based on dose by mass and the assumption that the "dose-makes-the-poison" (i.e. the weight-based dose) which we know is probably not valid for all nanomaterials (Stone ***et al.*** 2009). It is an ongoing discussion on which dose-metrics will be the best to use in nano(eco)toxicology. Furthermore, the process by which the color code is assigned to human hazards associated with the nanoform of a given material is based primarily on scientific expert judgement and a holistic assessment of the evidence of mutagenicity, carcinogenicity, respiratory toxicity, etc. As expert interpretation of the scientific literature can vary so can the conclusion reached and the human hazard color code assigned to nanomaterial. It is not possible to provide clear-cut guidance and rules at this point in time for how to complete a holistic evaluation of the human and environmental hazards associated with the nanoform of a given material. Although some might argue that this is something to strive and wish for, it could be argued that rigid rules would put a significant straitjacket on the emerging and exploratory field of nano(eco)toxicology and our ability to make decisions based on the newest available science.

Besides being helpful for users to sort out information and structure and communicate their knowledge, NanoRiskCat can furthermore be used to do a comparative analysis of two or more nanomaterials for the same application. Assuming, for instance, that the exposure profiles are the same for the two materials (i.e. ●●●), a comparative analysis of one or more alternatives would be narrowed down to an interpretation of the hazard profile of the two materials. To make a final conclusion about one being "more safe" than the other it is, however, necessary to take account of the respective concentrations of the nanomaterial in the products, the hazardous properties and the concentration of the other constituents in the products and whether there are any differences in the handling and the exposure potential between the products. Also it is important to evaluate if the identified hazards are associated to a specific exposure route and whether this exposure route is relevant for the product and its use i.e. whether a red spot for exposure match to a red spot for the hazard (same exposure route). Thus as a screening tool, NanoRiskCat gives an indication that has to be further verified before a final decision can be made.

5.3. Stakeholder-dependent uses of NanoRiskCat

Decisions that could come out of using NanoRiskCat are stakeholder-dependent. The tool in itself does not lead directly to a decision, but provides a more informed basis for decision-making by including a number of indica-

tors that define whether exposure and effects are likely (or unlikely) to occur and whether the nanomaterial may have harmful properties of concern.

Companies can use NanoRiskCat to communicate their knowledge about the exposure and effects of the nanomaterial they use by filling out the NanoRiskCat template and by making it available to interested parties. They could assess the need to develop guidance for safe uses that e.g. limit exposures and/or work systematically with designing safer applications of nanomaterials. Companies/designers could furthermore use NanoRiskCat to choose safer alternatives/applications of nanomaterials in their products.

Besides using NanoRiskCat as a screening tool to flag nanomaterial use of concern and hence subject for further investigation, regulators could use NanoRiskCat to set default guidance for when regulatory measures are to be implemented e.g. the need to consider implementation of precautionary measures that could be triggered by default if the color code of a given nanomaterial application is all red or if there are – say for instance -indications of high levels of environmental exposure and environmental hazards. Regulators could also decide to develop guidance on controlled uses. For instance, requirements could be made for the use of specific personal protection equipment if there is a high level of exposure to professional end-users. Finally, regulators could use NanoRiskCat to set research prioritizes for instance if there is an indication of high level of exposure, but a lot of "maybes" or unknowns in regard to human and environmental hazards.

Down-stream users (e.g. consumers) can use NanoRiskCat to make a preliminary assessment of a range of nanomaterials as a means to select the seemingly most benign material. Furthermore, independent parties such as academics and non-governmental organizations can use the tools to learn more about what companies know about exposure and effect of their nanomaterials and they can use NanoRiskCat to do their own evaluation and engage in an informed dialogue about nanorisks.

It is important to emphasize that it has not been possible within the framework of this project to make a further validation of the NRC concept. To promote a wider use of the tool it is considered necessary to perform additional case studies and if relevant adjust the processes and decision criteria in order to obtain a screening tool as informative and practical as possible.

6. Conclusion

This project was aimed at developing a conceptual framework for assisting manufacturers, down-stream end users, regulators and other stakeholders to evaluate, rank and communicate exposure and effect levels associated with the specific applications of a given nanomaterial. This is done through the framework NanoRiskCat by providing a detailed, qualitative, tiered approach for screening of indications of exposure and effects of nanomaterials. In NanoRiskCat exposure and effects are evaluated in the following sequence:

1. Exposure potential for professional end-users
2. Exposure potential for consumers
3. Exposure potential for the environment
4. A preliminary hazard evaluation for humans and
5. A preliminary hazard evaluation for the environment

A generic template for mapping and reporting these five aspects for a specific application of a given nanomaterial has been developed and can be found in Appendix 1 of this report.

In its simplest form the final outcome of using NanoRiskCat for a nanomaterial in a given application will be communicated in the form of a short title describing the use of the nanomaterial (e.g. MeO in ship paint) and a color code consisting of five dots (e.g, ●●●|●●) where the first three dots always refer to potential exposure of professional end-users, consumers and the environment in that sequence and the last two colors always refer to the hazard potential for humans and the environment. The colors signify whether the indications of exposures and effects separately are high (red), medium (yellow), low (green), or unknown (grey). To help communicate the scientific reasoning behind assigning a human health and environmental hazard classification and why a given nanomaterial was assigned red, yellow or grey, a number of default statements have been developed. These standard sentences are meant to reflect primarily whether the conclusion has been reached based on ***in vivo*** or ***in vitro*** studies and in regard to what endpoint. Depending to the final classification in regard to human health, the user of NRC has to select one or more of those sentences that best reflect the scientific basis for assigning the color code.

While the two cases included in this report by no means can be claimed to validate the NanoRiskCat, they serve a purpose is to illustrate illustrate the feasibility of NanoRiskCat. Thus, the two nanomaterials (titanium dioxide and C60-fullerenes) in two different applications i.e. C60 used in a lubricant and TiO_2 used in sunscreen were used as “training sets” for the conceptual framework. The NanoRiskCat code of C60 in lubricant was ●●●|●● based on ***in vitro*** evidence indicating at least one nanospecific human hazard and a nanomaterial specific LC_{50} or EC_{50} < 10 mg/l indicating environmental haz-

ard. For TiO_2 in sunscreen the NanoRiskCat code was ●●●|●● based on ***in vivo*** evidence indicating at least one nanospecific human hazard and a nanomaterial specific LC_{50} or EC_{50} < 10 mg/l indicating environmental hazard. It is evident that more cases are needed to show the strengths and weaknesses of NanoRiskCat, but this was beyond the scope of the present project.

The use of NanoRiskCat will in itself not lead directly to a decision, but provides a more informed basis for decision-making by including a number of indicators that defines whether exposures and effects are likely (or unlikely) to occur.

It is important to underline that NanoRiskCat is not a product label and NanoRiskCat is only to be used for evaluating the nanomaterial as an ingredient under the physical conditions it occurs in the product. NanoRiskCat does not evaluate exposure and effects from the other constituents and impurities in the product nor does it take into account the specific content of nanomaterial in the product. Thus, NanoRiskCat is directed towards the generic use descriptors and scenarios, which for instance are apparent in the product categories used in REACH. NanoRiskCat will contribute to safety guidance in relation of specific nanomaterial application and it is important to underline that filling out NanoRiskCat cannot be used to pass judgment about the safety of other (all) applications of a given nanomaterial. A strength of NanoRiskCat is that it can be used even in cases where lack of data is prominent and hampers the completion of traditional risk assessment procedures.

Decisions that could come out of using NanoRiskCat are stakeholder dependant. Regulators could use the tools to set default guidance for when regulatory measures are to be implemented, develop guidance on controlled uses and/or set research prioritizes. Companies can use NanoRiskCat to communicate what they know about the exposures and effects of the nanomaterial they use, assess the need to develop guidance for safe uses that e.g. limit exposures and/or work systematically with designing safer nanomaterials and use of these. Down-stream users (e.g. consumers) can use NanoRiskCat to make a preliminary assessment of a range of nanomaterials as a mean select the seemingly most benign material. Furthermore, independent parties such as academics and non-governmental organizations can use the tools to learn more about what companies known about exposure and effect of their nanomaterials and they can use NanoRiskCat to do their own evaluation and engage in an informed dialogue about nanorisks.

It is finally important to stress that the color coding obtained in NanoRiskCat should not be seen as an absolute categorization. It rather serves as a step in an iterative process in which stakeholders in risk-related issues can reach a common – and guided - understanding of the level of potential exposures and effects of nanomaterials in specific products.

It is important to emphasize that it has not been possible within the framework of this project to make a further validation of the NRC concept. To promote a wider use of the tool it is considered necessary to perform additional case studies and if relevant adjust the processes and decision criteria in order to obtain a screening tool as informative and practical as possible.

7. References

Baun, A., Hansen, S.F. 2008. Environmental challenges for nanomedicine. Nanomedicine 2(5): 605-608
.
Baun, A., Hartmann, N.B, Greiger, K.D., Hansen, S.F. 2009. Setting the Limits for Engineered Nanoparticles in European Surface Waters. Journal of Environmental Monitoring 11, 1774 – 1781.

BSI 2007a. Terminology for Nanofabrication. PAS 135:2007. London: BritishStandards Institution.

BSI 2007b. Terminology for Nanomaterials. PAS 136:2007. London: British Standards Institution.

CCA. 2008. Small Is Different: A Science Perspective On The Regulatory Challenges of the Nanoscale. Ottawa: The Council of Canadian Academies.

Davis, J.M., Wang, A., Sharkin, J.A. ***et al.*** 2009. External Review Draft Nanomaterial Case Studies: Nanoscale Titanium Dioxide in Water Treatment and in Topical Sunscreen. EPA/600/R-09/057. July 2009 National Center for Environmental Assessment Office of Research and Development U.S. Environmental Protection Agency Research Triangle Park, NC

ECHA 2008. Guidance on information requirements and chemical safety assessment Chapter R.7a: Endpoint specific guidance http://guidance.echa.europa.eu/docs/guidance_document/information_requirements_r7a_en.pdf?vers=02_02_10.

ECHA 2010. Guidance on information requirements and chemical safety assessment Chapter R.12 Use descriptor system. Version: 2 March 2010 http://guidance.echa.europa.eu/docs/guidance_document/information_requirements_r12_en.pdf).

EEA. 2001. Late Lessons from Early Warnings: The Precautionary Principle 1896–2000. Copenhagen: European Environmental Agency.

Environmental Defense and DuPont. 2007. Nano Risk Framework. Environmental,Defense and DuPont.

EP & CEU. 2008. REGULATION (EC) No 1272/2008 OF THE EUROPEAN PARLIAMENT AND OF THE COUNCIL of 16 December 2008 on classification, labelling and packaging of substances and mixtures, amending and repealing Directives 67/548/EEC and 1999/45/EC, and amending Regulation (EC) No 1907/2006, Official Journal of the European Union L 353/1-1355

Fisher, L. 2007. Envtl. Defense & DuPont to Jointly Launch Risk Framework. June 21 2007 available at http://www.wilsoncenter.org/ondemand/index.cfm?fuseaction=home.play&mediaid=A3F4AE5D□B21E□8EBB□069B78254ED2E9C4.

Genaidy, A., Sequeira, R., Rinder, M., A-Rehim, A. 2009. Risk analysis and protection measures in a carbon nanofiber manufacturing enterprise: An exploratory investigation. Science of the Total Environment 407: 5825–5838

Hansen, S.F., Larsen, B.H., Olsen, S.I., Baun, A. (2007). Categories and

Hazard Identification Scheme of Nanomaterials. Nanotoxicology, 3, 243-250.

Hansen, S.F., Michelson, E., Kamper, A., Borling, P., Stuer-Lauridsen, F. &

Baun, A. 2008, Categorization framework to aid exposure assessment of nanomaterials in consumer products, Ecotoxicology 17 (5): 438-447

Hansen, S.F. 2009. Regulation and Risk Assessment of Nanomaterials – Too Little, Too Late? (PhD Thesis). Kgs. Lyngby: DTU Environment. Available: http://www2.er.dtu.dk/publications/fulltext/2009/ENV2009-069.pdf [Accessed 17-04-2009].

Hansen, S.F. 2010. Multicriteria mapping of stakeholder preferences in regulating nanotechnology Journal of Nanoparticle Research 12:1959–1970

Hougaard KS, Jackson P, Jensen KA, Sloth JJ, Löschner K, Larsen EH, Birkedal RK, Vibenholt A, Boisen AMZ, Wallin H, Vogel U (2010) Effects of prenatal exposure to surface-coated nanosized titanium dioxide (UV-Titan). Particle Fibre Toxicol 14;7:16.

Höck J., Epprecht T., Hofmann H., Höhner K., Krug H., Lorenz C., Limbach L., Gehr P., Nowack B., Riediker M., Schirmer K., Schmid B., Som C., Stark W., Studer C., Ulrich A., von Götz N., Wengert S., Wick P.: Guidelines on the Precautionary Matrix for Synthetic Nanomaterials. Federal Office of Public Health and Federal Office for the Environment, Berne 2010, Version 2.Available: http://www.bag.admin.ch/themen/chemikalien/00228/00510/05626/index.html?lang=en
(Accessed 17 May 2010)

Industriens Branchearbejdsmiljøråd. 2011. NANOSAFER Nanopartikler i arbejdsmiljøet. Available: http://www.i-bar.dk/NANOSAFER.aspx (Accessed 14-03-2011)

ISO 2008. Nanotechnologies - Terminology and definitions for nano-objects - Nanoparticle, nanofibre and nanoplate. ISO/TS 27687:2008. Geneva: International Organization for Standardization.

Linkov, I., Satterstrom, F.K., Steevens, J., Ferguson, E., Pleus, R.C. 2007. Multi-criteria decision analysis and environmental risk assessment for nanomaterials. Journal of Nanoparticle Research 9:543–554.

Meldrum, M. 1996. Review of Fibre Toxicology (OELs). Health& Safety Executives. Sudbury, Suffolk; Health& Safety Executives (summary available: http://www.asbestos-institute.ca/reviews/hse/hse-sum.html, accessed 08-09-2010)

Nielsen GD, Roursgaard M, Jensen KA, Poulsen, SS, Larsen ST. In vivo biology and toxicology of fullerenes and their derivatives. Basic Clin Pharmacol Toxicol 2008;103(3):197-208

OECD 1992. OECD Guideline for Testing of Chemicals 301 Adopted: 17.07.92 Ready Biodegradability. Available: http://www.oecd-library.org/docserver/download/fulltext/9730101e.pdf?expires=1303986661&id=id&accname=freeContent&checksum=FD9FA7BFD60C66B90BBFA3B5F61B2562 (Accessed 25-04-2011)

OECD 2011. OECD Guidelines for the Testing of Chemicals, Section 3: Degradation and Accumulation. Available: http://www.oecd-ilibrary.org/environment/oecd-guidelines-for-the-testing-of-chemicals-section-3-degradation-and-accumulation_2074577x (Accessed 25-04-2011)

Paik. S.Y., Zalk, D.M., Swuste, P. 2008. Application of a Pilot Control Banding Tool for Risk Level Assessment and Control of Nanoparticle Exposures. Ann. Occup. Hyg. 52(6): 419–428.

RCEP. 2008. Twenty-seventh Report Novel Materials in the Environment: The case of nanotechnology Royal Commission on Environmental Pollution. Norwich: The Stationery Office

Shinohara, N., Nakamishi, J., Gamo, M. 2009. Risk Assessment of Manufactured Nanomaterials – C60. Available: http://www.aist-riss.jp/main/modules/product/nano_rad.html?ml_lang=en (Accessed July 15, 2010)

Stone, V., Hankin, S., Aitken, R., Aschberger, K., Baun, A., Christensen, F., Fernandes, T., Hansen, S.F., Hartmann, N.B., Hutchinson, G., Johnston, H., Micheletti, G., Peters, S., Ross, B., Sokull-Kluettgen, B., Stark, D., Tran, L. 2009. Engineered Nanoparticles: Review of Health and Environmental Safety (ENRHES). Available: http://nmi.jrc.ec.europa.eu/project/ENRHES.htm (Accessed February 1, 2010).

Stuer-Lauridsen, F., Kamper, A., Borling P., Petersen, G.I., Hansen, S.F., Baun, A. 2007. Mapping of products containing nanoparticles or based on nanotechnology, Mapping of Chemical Substances in Consumer Products, No. 81, 2007, Danish EPA. Available: http://www2.mst.dk/common/Udgivramme/Frame.asp?pg=http://www2.mst.dk/Udgiv/publications/2007/978-87-7052-536-7/html/default_eng.htm

Tervonen, T., J. Figueira, J. Steevens, J. Kim, and I. Linkov. (2009). Risk-based classification system of nanomaterials. Journal of Nanoparticle Research 11:757–766

The Danish Working Environment Authority 2002. C.0.1 October 2002 Limit values for substances and materials.
http://www.at.dk/~/media/AT/at/Engelsk-pdf/At-vejledninger/GVlisteUK%20pdf.ashx
(Accessed 25-04-2011)

Tran CL, SM Hankin, B Ross, RJ Aitken, AD Jones, K Donaldson, V Stone, R Tantra, 2008, 'An outline scoping study to determine whether high aspect ratio nanoparticles (HARN) should raise the same concerns as do asbestos fibres', Report on DEFRA project CB0406

Tønning, K., Poulsen, M. 2007. Nanotechnology in the Danish industry - survey on production and application. Environmental Project No. 1206 2007. 2007. Copenhagen: Danish Ministry of the Environment Danish Environmental Protection Agency.

UNEP 2009. Globally Harmonized System of Classification and Labelling of Chemicals (GHS) Third revised edition United Nations, 2009. Available:
http://live.unece.org/trans/danger/publi/ghs/ghs_rev03/03files_e.html
(Accessed 25-04-2011)

Wikipedia 2011. Phagocyte. Avialable:
http://en.wikipedia.org/wiki/Phagocyte#cite_ref-117
(Accessed 25-04-2011)

Zaik, D., Paik, S.Y., Swuste, P. 2009. Evaluating the Control Banding Nanotool: a qualitative risk assessment method for controlling nanoparticle exposures. J Nanopart Res 11:1685-1704.

APPENDIX 1: NanoRiskCat●●●|●● Template

Subject: <<Insert short title here>> produced by <<Company name>>

Nanomaterial description	
Material source or producer:	<< Insert source of the nanomaterial used in the product. This could be the name of primary producer of the nanomaterial, the distributor, etc.>>
Manufacturing process:	<< If known, the process used to manufacture the nanomaterial should be reported here This could e.g. arc method, chemical vapor deposition, etc. >>
Appearance:	<< Describe the visual appearance of the nanomaterial here e.g. black powder, yellow paste, transparent liquid >>
Chemical composition:	<< Insert chemical formula here e.g. C60, TiO2 >>
Physical form/shape:	<< Insert physical form and shape of the nanomaterial e.g. Powder/spherical, paste/tubes >>
Purity:	<< Insert purity of the nanomaterials e.g. 99.5% >>
Size distribution:	<< Insert primary particle size distribution of the nanomatereal subject for the **NanoRiskCat●●●|●●** >>
Solubility:	<< Insert the solubility of the nanomaterial in

	water e.g. 1.3×10^{-11} mg/mL >>
State of aggregation or agglomeration:	<< Insert state of aggregation or agglomeration e.g. 85-140 nm >>
CAS number (if applicable):	<< Insert CAS number if specifically relevant for the nanomaterial in question >>
Product description	
<< Insert a description of the product including chemical composition (w/w%) of the product subject to the **NanoRiskCat** as well as the purpose of adding the nanomaterial and it's function in the product >>	

Applications

<< Insert information on how the product subject to the **NanoRiskCat**●●●|●● should be used, why the product should be used, how often and duration of the product. Any personal protection equipment, precautions and/or rules of conduct should also be inserted here. Possible routes of exposure to humans and the environment should be clearly stated and so should any recommended measures to prevent exposure. If OELs and PEC/PNECs have been established for the product subject to the **NanoRiskCat**●●●|●● these should be listed here as well as the source of these >>

Exposure potential for professional end-users

According to table 4 in chapter 3 of the **NanoRiskCat**●●●|●● guidance document on Criteria for evaluating the exposure profile, the following REACH Use Descriptor Categories are relevant for <<insert product name>>.

REACH Cat.	#	Description	Examples and explanations
PROC	<<Insert number of first relevant PROC >>	<<Insert PROC description>>	<<Insert PROC examples and explanations>>
PC	<<Insert number of first relevant PC >>	<<Insert PC description>>	<<Insert PC examples and explanations>>
FC	<<Insert number of first relevant PC >>	<<Insert FC description>>	<<Insert FC examples and explanations>>

<<Insert the number, description, examples and explanations of the relevant PROCs, PCs and FCs in the table above. Add rows so that each relevant PROC, PC and FC is located in its own row. Number, description and examples and explanation associated with each PROC, PC, and FC can be found in the tables of appendix 3. The color of the PROC, PC and FC in the tables of appendix 3 should also be indicated here by shading the row.>>

Exposures to the professional end-users of <<Insert product name>> are <<Insert statement about the number of potential exposures e.g. “multiple”, “limited”, “minor”, etc.>> and to <<Insert whether exposure is to be expected or not e.g. “be expected”, “not to be expected”,

etc.>>. The main contact zones with <<Insert product name>> are <<Insert main contact zones e.g. “the hands”, “eyes”, etc>>.

<<Insert note about PCs, AC, no intended release and AC, intended release that are not relevant or fall outside the scope of intended uses of the product subject to this report>>

Considering the color-codes of the PROC(s) (<<Insert bullet (Font 12, times new roman)>>), PC(s) (<<Insert bullet (Font 12, times new roman)>>) and FC(s) (<<Insert bullet (Font 12, times new roman)>>), we concluded that the overall

Exposure potential for professional end-users is <<Insert bullet (Font 20, times new roman) with the color that best summarizes the color of the PROC(s), PC(s) and FC(s) in the table above>>

Consumer exposure potential

According to table 4 in chapter 3 of the **NanoRiskCat**●●●|●● guidance document on Criteria for evaluating the exposure profile, the following REACH Use Descriptor Categories are relevant for <<Insert product name>>.

REACH Cat.	**#**	**Description**	**Examples and explanations**
PC	<<Insert number of first relevant PC >>	<<Insert PC description>>	<<Insert PC examples and explanations>>
AC, no intended release	<<Insert number of first AC, no intended release >>	<< Insert description of AC, no intended release >>	<< Insert examples and explanations of AC, no intended release >>
AC, intended release	<<Insert number of first AC, intended release >>	<< Insert description of AC, intended release >>	<<Insert examples and explanations of AC, intended release >>

<<Insert the number, description, examples and explanations of the relevant PCs, AC, no intended and AC, intended release in the table above. Add rows so that each relevant PC, AC, no intended release and AC, intended release is located in it's own row. Number, description and examples and explanation associated with each PC, AC, no intended release and AC, intended release can be found in the tables of appendix 3. The color of the AC, no intended release and AC, intended release in the tables of appendix 3 should also be indicated here by shading the row>>.

Consumer exposure to <<Insert product name>> are <<Insert statement about the number of potential exposures e.g. "multiple", "limited", "minor", etc.>> and to <<Insert whether exposure is to be expected or not e.g. "be expected", "not to be expected", etc.>>. The main contact zones with <<Insert product name>> are <<Insert main contact zones e.g. "the hands", "eyes", etc>>.

<<Insert note about PCs, AC, no intended release and AC, intended release that are not relevant or fall outside the scope of intended uses of the product subject to this report>>

Considering the color-codes of the PC (<<Insert bullet (Font 12, times new roman)>>), AC, no intended release (<<Insert bullet (Font 12, times new roman)>>) and AC, intended release (<<Insert bullet (Font 12, times new roman)>>), we concluded that the overall

Consumer exposure potential is <<Insert bullet (Font 20, times new roman) with the color that best summarizes the color of the PC, AC, no intended release and AC, intended release in the table above>>

Environmental exposure potential

According to table 4 in chapter 3 of the **NanoRiskCat** guidance document on Criteria for evaluating the exposure profile, the following REACH Use Descriptor Categories are relevant for <<Insert product name>>.

REACH Cat.	#	Description	Examples and explanations
PC	<<Insert number of first relevant PC >>	<<Insert description for this PC>>	<<Insert examples and explanations for this PC>>
AC, no intended release	<<Insert number of first relevant AC, no intended release >>	<<Insert description of this AC, no intended release >>	<<Insert examples and explanations for this AC, no intended release >>
AC, intended release	<<Insert number of first relevant AC, intended release >>	<<Insert description of this AC, intended release >>	<<Insert examples and explanations for this AC, intended release >>

<<Insert the number, description, examples and explanations of the relevant AC, no intended release, AC, intended release and ERC in the table above. Add rows so that each relevant AC, no intended release, AC, intended release and ERC is located in it's own row. Number, description and examples and explanation associated with each AC, no intended, AC, intended release and ERC can be found in the tables of appendix 3. The color of the AC, no intended release, AC, intended release and ERC in the tables of appendix 3 should also be indicated here by shading the row>> Environmental exposure to <<Insert product name>> are <<Insert statement about the number of potential exposures e.g. "multiple", "limited", "minor", etc.>> and to <<Insert whether exposure is to be expected or not e.g. "be expected", "not to be expected", etc.>>. The main outlets to the environment are expected to be <<Insert expected fate of nanomaterial in question, e.g. direct into the water recipients and/or indirectly via the STPs into water recipient and soil>>.

<<Insert note about AC, no intended, AC, intended release and ERC that are not relevant or fall outside the scope of intended uses of the product subject to this report>>

Considering the color-codes of the AC, no intended release (<<Insert bullet (Font 12, times new roman)>>), AC, intended release(s) (<<Insert bullet (Font 12, times new roman)>>) and ERC(s) (<<Insert bullet (Font 12, times new roman)>>), we concluded that the overall

Environmental exposure potential is <<Insert bullet (Font 20, times new roman) with the color that best summarizes the color of the AC, no intended release(s) and AC, intended release(s)

and ERC in the table above>>

Literature methodology/sources of information

The following sources of information were used to fill out the **NanoRiskCat** for <<Insert chemical formula as for nanomaterial used in the product subject of this report >>:

1. <<Insert references in bullets for the information that is cited when filling out the information requirements on human health and environment. This can be either scientific reviews published by international, well-recognized and independent scientific experts or primary literature identified through web of science, pubmed or the ICON database on nanomaterial EHS. If the latter, clearly state which database were used and the search terms used>>.

Human hazard profile

1. **HARN: Does the nanomaterial fulfill the HARN paradigm?**

   Answer: <<Insert either "Yes", "Maybe", "No" or "No information">>

   Arguments and explanation: <<Provide argument and explanation for the why/why not the nanomaterial in question does or does not fulfill the HARN paradigm >>

2. **Bulk – "Level A CLP": Is the bulk form of the nanomaterial known to cause or may cause serious damaging effects?**

   Answer: <<Insert either "Yes", "Maybe", "No" or "No information">>

   Arguments and explanation: <<Provide argument and explanation for the why/why not the nanomaterial in question is not known to cause or may cause serious damaging effects>>

3. **Bulk – "Level B CLP": Is the bulk form of the nanomaterial classified for other less adverse effects according to the CLP?**

   Answer: <<Insert either "Yes", "Maybe", "No" or "No information">>

   Arguments and explanation: <<Provide argument and explanation for the why/why not

the nanomaterial in question is not suspected to cause or may cause serious damaging effects>>

4. **Nano – Acute tox: Is the specific nanomaterial known to be acute toxic?**

Answer: <<Insert either "Yes", "Maybe", "No" or "No information">>

Arguments and explanation: <<Provide a short summary of the scientific evidence in regard to acute toxicity and provide references>>

5. **Are there indications that the nanomaterial causes genotoxic-, mutagenic-, carcinogenic-, respiratory-, cardiovascular, neurotoxic or reproductive effects in humans and/or laboratory animals or has organ-specific accumulation been documented?**

Answer: <<Insert either "Yes", "Maybe", "No" or "No information">>

Arguments and explanation:

a. Genotoxicity and mutagenicity: <<Provide a short summary of the scientific evidence in regard to genotoxicity and mutagenicity and provide references>>

b. Respiratory tract toxicity: <<Provide a short summary of the scientific evidence in regard to respiratory toxicology and provide references>>

c. Cardiovascular toxicity: <<Provide a short summary of the scientific evidence in regard to cardio-vascular effects and provide references>>

d. Neurotoxicity: <<Provide a short summary of the scientific evidence in regard to neurotoxicity and provide references>>

e. Reproductive damage:

<<Provide a short summary of the scientific evidence in regard to reproductive damage

and provide references>>

f. Carcinogenicity: <<Provide a short summary of the scientific evidence in regard to carcinogenicity and provide references>>

g. Organ-specific accumulation: <<Provide a short summary of the scientific evidence in regard to organ-specific accumulation and provide references>>

6. Overall evaluation of human hazard

The overall answer to this question is <<Insert either "Yes", "Maybe", "No" or "No information">> based on the following considerations:

1. << Provide a short summary and explain the reasoning in bullets behind the derivation of the overall evaluation >>

We conclude that the color-code that best reflects the human hazard profile of <<nanomaterial used in product subject to this report>> used in <<product name>> is <<Insert bullet (Font 20, times new roman) with the color that best summarizes the evidence provided above>> based on <<Insert the defaults sentences appendix 2, table 2.1 that describes the nature of the evidence that provides that basis for deriving the color code for human health hazard in NanoRiskCat>>

Environment hazard profile

1. **Bulk – "Level 1 CLP": Is the bulk form of the nanomaterial classified as CLP Acute 1 or Chronic 1 or Chronic 2?**

   Answer: <<Insert either "Yes", "Maybe", "No" or "No information">>

   Arguments and explanation: <<Provide argument and explanation for the why/why not the nanomaterial in question is classified as CLP Acute 1 or Chronic 1 or Chronic 2>>

2. **Nano – LC_{50}<10 mg/l: Is the nanomaterial in question reported to be hazardous to environmental species i.e. LC50 or EC 50 <10 mg/l?**

   Answer: <<Insert either "Yes", "Maybe", "No" or "No information">>

   Argument and explanation: <<Provide a short summary of the scientific evidence in regard to environmental hazards that have established reported LC50 or EC50 on various species after exposure to the nanomaterials subject to the NRC>>

3. **Bulk – "Level 2 CLP": Is the bulk form of the nanomaterial classified as CLP Chonic 3 or Chronic 4 or documented nano-specific effects?**

   Answer: <<Insert either "Yes", "Maybe", "No" or "No information">>

   Arguments and explanation: <<Provide argument and explanation for the why/why not the nanomaterial in question is not classified as CLP Chronic 3 or Chronic 4 or does not cause significant effects for which EC50 or LC50 values cannot be established or non-standardized endpoints have been applied>>

4. **Nano – LC_{50}<100 mg/l: Is the nanomaterial in question reported to be hazardous to environmental species i.e. LC50 or EC 50 <10 mg/l?**

   Answer: <<Insert either "Yes", "Maybe", "No" or "No information">>

   Argument and explanation: <<Provide a short summary of the scientific evidence in regard to environmental hazards that have established reported LC50 or EC50 on various species after exposure to the nanomaterials subject to the NRC>>

5. **$T_{½}$>40 days: Is the nanomaterial in question persistent i.e. T½>40 days?**

   Answer: <<Insert either "Yes", "Maybe", "No" or "No information">>

Argument and explanation: <<Provide argument and explanation for the why/why not the nanomaterial in question is or is not persistent and provide references>>

6. **BCF>50: Is the nanomaterial in question bioaccumulative i.e. BCF>50?**

   Answer: <<Insert either "Yes", "Maybe", "No" or "No information">>

   Argument and explanation: << Provide argument and explanation for the why/why not the nanomaterial in question does/does not accumulate and provide references >>

7. **Dispersive or long-range transport, ecosystem effects?**

   Answer: <<Insert either "Yes", "Maybe", "No" or "No information">>

   Argument and explanation: <<Provide a short summary of the evidence identified in regard to whether the nanomaterial used in the product subject to this report could lead to irreversible harm to the environment and provide references>>

8. **Is the nanomaterial dispersive?**

   Answer: <<Insert either "Yes", "Maybe", "No" or "No information">>

   Argument and explanation: << Provide argument and explanation for the why/why not the nanomaterial in question is or is not readily dispersed and provide references Provide a short summary of the scientific evidence in regard >>

9. **Novelty**

   Answer: <<Insert either "Yes", "Maybe", "No" or "No information">>

   Argument and explanation: << Provide arguments and explain to which extend humans and environment have previously been exposed to the nanomaterials subject to the NRC

10. **Overall evaluation of environmental hazard**

We conclude that the color-code that best reflects the environmental hazard profile of <<nanomaterial used in product subject to this report>> used in <<product name>> is <<Insert bullet (Font 20, times new roman) with the color that best summarizes the evidence provided above>> based on <<Insert the defaults sentences in appendix 2, table 2.2 that describes the nature of the evidence that provides that basis for deriving the color

code for environmental hazard in NanoRiskCat>>

Summary

This information provided and summarized in this template is considered to be accurate at the date of printing and is believed to be a complete reflection of what the <<Insert company name>> knows about the risks of using <<chemical formula of the nanomaterials used in the product subject to this report>> to <<function of the nanomaterial in the product subject to the report>> of <<product name>>.

Exposure			Effects	
Prof	**Consum**	**Environ**	**Human**	**Environ**
<Insert colored bullet for prof exp>	<Insert colored bullet for con exp>	<Insert colored bullet for env exp>	<Insert Colored bullet for hum haz>	<Insert Colored bullet for env haz>
			<< Insert standard sentence number>>[a)]	<< Insert standard sentence number>>[b)]

Red, yellow and green indicate high, medium and low indication of exposure/effect level whereas gray indicates too limited data to assess exposure/effect; a) see Appendix 2, Table A2.1; b) see Appendix 2, Table A2.2.

The overall **NanoRiskCat**code for the <<insert chemical formula of nanomaterial>> in <<product name>> is <<provide list of colored bullet reflecting the conclusions made about exposure potential for professional end-users, consumers, and the environment as well as the conclusions made about the human and environmental hazard profiles>>

NanoRiskCat does not lead directly to a decision, but provides a basis for decision-making by defining a number of concrete criteria that defines to which extend there are indication of exposures and effects for professional users, consumers, and the environment

It is the reader's obligation to evaluate this **NanoRiskCat** in the light of any new scientific evidence regarding risks published after the data of printing and to comply with all applicable laws and regulations.

Date of printing	**Signature**
…<<Insert date/month/year>>**……**	**……**<<Signature of company rep.>>**…**

APPENDIX 2. Additional sentences to explain the color codes in NanoRiskCat.

Table A2.1 Additional sentences to explain the color code for human health hazard in NanoRiskCat.

Sentence no.	Color	Description
1	Red	"based evidence of HARN"
2	Red	"based on bulk CLP classification 1-4 for acute toxicity"
3	Red	"based on CLP classification 1 for skin corrosion/irritation, eye damage/irritation/respiratory and skin sentization"
4	Red	"based on bulk CLP classification 1 or 2 germ cell mutagenicity/carcinogenicity, reproductive toxicity, specific target organ toxicity
5	Red	"based on bulk CLP classification 1 for aspiration toxicity"
6	Red	"based on nano acute tox"
7	Red	a. "based on *in vivo* evidence of effects when testing the nanomaterial (genotox/mutagenicity, respiratory effects, cardio-vascular effects, acute neurotoxic effects, reproductive damage, carcinogenicity, organ accumulation)
		b. "based on *in vivo* evidence of a combination of hazards from testing of the nanomaterial"
8	Red	a. "based on *in vitro* evidence of effects when testing the nanomaterial (genotox/mutagenicity, respiratory effects, cardio-vascular effects, acute neurotoxic effects, reproductive damage, carcinogenicity, organ accumulation)
		b. "based on *in vitro* evidence of a combination of hazards from testing of the nanomaterial"
9	Red	"based on bulk classified as a CLP category 2 in regard to skin corrosion/irritation/ serious eye damage/irritation as well as *in vivo* evidence of hazards from testing of the nanomaterial"
10	Red	"based on bulk classified as a CLP category 3 in regard to specific target organ toxicity - single exposure as well as *in vivo* evidence of hazards from testing of the nanomaterial"
11	Red	"based on bulk classified as a CLP category 2 in regard to skin corrosion/irritation/ serious eye damage/irritation as well as *in vitro* evidence of hazards from testing of the nanomaterial"
12	Red	"based on bulk classified as a CLP category 3 in regard to specific target organ toxicity - single exposure as well as *in vitro* evidence of hazards from testing of the nanomaterial"
13	Yellow	"based on *in vivo* evidence indicating at least one hazard from testing of the nanomaterial"
14	Yellow	"based on *in vitro* evidence indicating at least one hazard from testing of the nanomaterial"
15	Yellow	"based on bulk classified as a CLP category 2 in regard to skin corrosion/irritation/ serious eye damage/irritation as well as evidence of no hazards from testing of the nanomaterial"
16	Yellow	"based on bulk classified as a CLP category 3 in regard to specific target organ toxicity - single exposure as well as evidence of no hazards from testing of the nanomaterial"
17	Yellow	"based on bulk classified as a CLP category 2 in regard to skin corrosion/irritation/ serious eye damage/irritation as well as not enough data on possible hazards from testing of the nanomaterial"
18	Yellow	" based on bulk classified as a CLP category 3 in regard to specific target organ toxicity - single exposure as well as not enough data on possible hazards from testing of the nanomaterial"
19	Grey	"based on not enough *in vitro* and/or *in vivo* data being available on hazards from testing of the nanomaterial"

Table A2.2 Additional sentences to explain the color code for environmental effects in NanoRiskCat.

Sentence no.	Color	Description
1	Red	"based on bulk CLP classification of Acute 1 or Chronic 1 or Chronic 2"
2	Red	"based on nanospecific LC50 or EC50 < 10 mg/l"
3	Red	"based on possible or confirmative evidence of nanospecific LC50 or EC50 < 100 mg/l and T1/2 > 40 d"
4	Red	"based on possible or confirmative evidence of nanospecific LC50 or EC50 < 100 mg/l and BCF > 50"
5	Red	"based on evidence of T1/2 > 40 d and a BCF > 50"
6	Red	a. "based on bulk CLP classification of Chronic 3 or Chronic 4 and nanospecific effects (LC50/EC50 < 100 mg/l or T½>40d or BCF>50)
		b. "based on bulk CLP classification of Chronic 3 or Chronic 4 and T1/2 > 40 d and a BCF > 50"
		c. "based on bulk CLP classification of Chronic 3 or Chronic 4 and an evaluation of dispersive or long range transport, ecosystem effects and novelty"
8	Yellow	"based on a BCF > 50"
9	Yellow	"based on an evaluation of dispersive or long range transport, ecosystem effects and novelty"
10	Yellow	"based on bulk CLP classification of Chronic 3 or Chronic 4 and an evaluation of dispersive or long range transport, ecosystem effects and novelty"
11	Grey	"based on an evaluation of dispersive or long range transport, ecosystem effects and novelty"
12	Grey	"based on bulk CLP classification of Chronic 3 or Chronic 4 and an evaluation of dispersive or long range transport, ecosystem effects and novelty"

APPENDIX 3. Default colors assigned to REACH Use Descriptor Categories

Table 3.1 Default colors assigned to Process categories [PROC]

	Process categories	Examples and explanations
PROC1	Use in closed process, no likelihood of exposure	Use of the substances in high integrity contained system where little potential exists for exposures, e.g. any sampling via closed loop systems
PROC2	Use in closed, continuous process with occasional controlled exposure	Continuous process but where the design philosophy is not specifically aimed at minimizing emissions It is not high integrity and occasional expose will arise e.g. through maintenance, sampling and equipment breakages
PROC3	Use in closed batch process (synthesis or formulation)	Batch manufacture of a chemical or formulation where the predominant handling is in a contained manner, e.g. through enclosed transfers, but where some opportunity for contact with chemicals occurs, e.g. through sampling
PROC4	Use in batch and other process (synthesis) where opportunity for exposure arises	Use in batch manufacture of a chemical where significant opportunity for exposure arises, e.g. during charging, sampling or discharge of material, and when the nature of the design is likely to result in exposure
PROC5	Mixing or blending in batch processes for formulation of preparations* and articles (multistage and/or significant contact)	Manufacture or formulation of chemical products or articles using technologies related to mixing and blending of solid or liquid materials, and where the process is in stages and provides the opportunity for significant contact at any stage
PROC6	Calendering operations	Processing of product matrix Calendering at elevated temperature an large exposed surface
PROC7	Industrial spraying	Air dispersive techniques Spraying for surface coating, adhesives, polishes/cleaners, air care products, sandblasting Substances can be inhaled as aerosols. The energy of the aerosol particles may require advanced exposure controls; in case of coating, overspray may lead to waste water and waste.
PROC8a	Transfer of substance or preparation (charging/ discharging) from/to vessels/large containers at non-dedicated facilities	Sampling, loading, filling, transfer, dumping, bagging in non-dedicated facilities. Exposure related to dust, vapour, aerosols or spillage, and cleaning of equipment to be expected.
PROC8b	Transfer of substance or preparation (charging/discharging) from/to vessels/large containers at dedicated facilities	Sampling, loading, filling, transfer, dumping, bagging in dedicated facilities. Exposure related to dust, vapour, aerosols or spillage, and cleaning of equipment to be expected.

PROC9	Transfer of substance or preparation into small containers (dedicated filling line, including weighing)	Filling lines specifically designed to both capture vapour and aerosol emissions and _tomizat spillage
PROC10	Roller application or brushing	Low energy spreading of e.g. coatings Including cleaning of surfaces. Substance can be inhaled as vapours, skin contact can occur through droplets, splashes, working with wipes and handling of treated surfaces.
PROC11	Non industrial spraying	Air dispersive techniques Spraying for surface coating, adhesives, polishes/cleaners, air care products, sandblasting Substances can be inhaled as aerosols. The energy of the aerosol particles may require advanced exposure controls.
PROC12	Use of blowing agents in manufacture of foam	
PROC13	Treatment of articles by dipping and pouring	Immersion operations Treatment of articles by dipping, pouring, immersing, soaking, washing out or washing in substances; including cold formation or resin type matrix. Includes handling of treated objects (e.g. after dying, plating,). Substance is applied to a surface by low energy techniques such as dipping the article into a bath or pouring a preparation onto a surface.
PROC14	Production of preparations* or articles by tabletting, compression, extrusion, pelletisation	Processing of preparations and/or substances (liquid and solid) into preparations or articles. Substances in the chemical matrix may be exposed to elevated mechanical and/or thermal energy conditions. Exposure is predominantly related to volatiles and/or generated fumes, dust may be formed as well.
PROC15	Use as laboratory reagent	Use of substances at small scale laboratory (< 1 l or 1 kg present at workplace). Larger laboratories and R+D installations should be treated as industrial processes.
PROC16	Using material as fuel sources, limited exposure to unburned product to be expected	Covers the use of material as fuel sources (including additives) where limited exposure to the product in its unburned form is expected. Does not cover exposure as a consequence of spillage or combustion.
PROC17	Lubrication at high energy conditions and in partly open process	Lubrication at high energy conditions (temperature, friction) between moving parts and substance; significant part of process is open to workers. The metal working fluid may form aerosols or fumes due to rapidly moving metal parts.
PROC18	Greasing at high energy conditions	Use as lubricant where significant energy or temperature is applied between the substance and the moving parts

PROC19	Hand-mixing with intimate contact and only PPE available	Addresses occupations where intimate and intentional contact with substances occurs without any specific exposure controls other than PPE.
PROC20	Heat and pressure transfer fluids in dispersive, professional use but closed systems	Motor and engine oils, brake fluids Also in these applications, the lubricant may be exposed to high energy conditions and chemical reactions may take place during use. Exhausted fluids need to be disposed of as waste. Repair and maintenance may lead to skin contact
PROC21	Low energy manipulation of substances bound in materials and/or articles	Manual cutting, cold rolling or assembly/disassembly of material/article (including metals in massive form), possibly resulting in the release of fibres, metal fumes or dust
PROC22	Potentially closed processing operations with minerals/metals at elevated temperature Industrial setting	Activities at smelters, furnaces, refineries, coke ovens. Exposure related to dust and fumes to be expected. Emission from direct cooling may be relevant.
PROC23	Open processing and transfer operations with minerals/metals at elevated temperature	Sand and die casting, tapping and casting melted solids, drossing of melted solids, hot dip _tomization, raking of melted solids in paving Exposure related to dust and fumes to be expected
PROC24	High (mechanical) energy work-up of substances bound in materials and/or articles	Substantial thermal or kinetic energy applied to substance (including metals in massive form) by hot rolling/forming, grinding, mechanical cutting, drilling or sanding. Exposure is predominantly expected to be to dust. Dust or aerosol emission as result of direct cooling may be expected.
PROC25	Other hot work operations with metals	Welding, soldering, gouging, brazing, flame cutting Exposure is predominantly expected to fumes and gases.
PROC26	Handling of solid inorganic substances at ambient temperature	Transfer and handling of ores, concentrates, raw metal oxides and scrap; packaging, unpackaging, mixing/blending and weighing of metal powders or other minerals23
PROC27a	Production of metal powders (hot processes)	Production of metal powders by hot metallurgical processes (_tomization, dry dispersion)24
PROC27b	Production of metal powders (wet processes)	Production of metal powders by wet metallurgical processes (electrolysis, wet dispersion)25

Table 3.2 Default colors assigned to Chemical Product Category (PC)

	Category for describing market sectors (at supply level) regarding all uses (workers and consumers)	**Examples and explanations**	Location of nanoelement		Ref
PC1	Adhesives, sealants		Suspended in liquids (IIIb)		http://www.nanotechproject.org/inventories/consumer/browse/products/6806/ http://www.nanotechproject.org/inventories/consumer/browse/products/nano_glue/
PC2	Adsorbents		Surface bound (IIIa)		http://www.nanotechproject.org/inventories/consumer/browse/products/geohumus_soil_wetting_agent/ http://en.wikipedia.org/wiki/Adsorption#Adsorbents http://nanopatentsandinnovations.blogspot.com/2010/01/honeywelluop-reveal-nano-adsorbents.html
PC3	Air care products		Airborne (IIId)		http://www.healthycleaning101.org/english/ACP_pub.html
PC4	Anti-Freeze and de-icing products		Suspended in liquids (IIIb)	Airborne (IIId)	http://www.nanotechproject.org/inventories/consumer/browse/products/nano_car_sealing_rims_9/ http://www.nauticexpo.com/prod/star-brite/anti-freeze-coolant-additive-21539-49549.html www.cryotech.com/products/runway.php
PC7	Base metals and alloys		Suspended in solid (IIIc)		http://www.nanotechproject.org/inventories/consumer/search/?keywords=disinfectant&company=0&country_origin=0&categories=0&subcategories=0&created=&modifie

					d=&search=1
PC8	Biocidal products (e.g. Disinfectants, pest control)	PC 35 should be assigned to disinfectants being used as a component in a cleaning product	Surface bound (IIIa)	Suspended in liquids (IIIb)	http://www.nanotechproject.org/inventories/consumer/search/?keywords=paint&company=0&country_origin=0&categories=0&subcategories=0&created=&modified=&search=1
PC9a	Coatings and paints, thinners, paint removers		Suspended in liquids (IIIb)		
PC9b	Fillers, putties, plasters, modelling clay		Suspended in liquids (IIIb)		
PC9c	Finger paints		Suspended in liquids (IIIb)		http://www.911review.com/energeticmaterials09/videnskab/DanishScientist.html
PC11	Explosives		Suspended in liquids (IIIb)		http://www.agronano.com/nanogro.htm http://www.alibaba.com/product-free/107088915/Iron_Chelate_Fertilizer_nano_technology_.html
PC12	Fertilizers		Suspended in liquids (IIIb)		http://www.nanotechproject.org/inventories/consumer/browse/products/4970/ http://www.nanotechproject.org/inventories/consumer/browse/products/nanotech_eefuel_additive/
PC13	Fuels		Suspended in liquids (IIIb)		
PC14	Metal surface treatment products, including galvanic and electroplating products	This covers substances permanently binding with the metal surface	Suspended in liquids (IIIb)	Surface bound (IIIa)	
PC15	Non-metal-surface treatment products	Like for example treatment of walls before painting.	Suspended in liquids (IIIb)	Surface bound (IIIa)	http://www.sciencedirect.com/science?_ob=ArticleURL&_udi=B6V1Y-4JTRTK7-3&_user=10&_coverDate=12%2F31%2F2006&_rdoc=1&_fmt=high&_orig=search&_sort=d&_docanchor=&view=c&_searchStrId=1343317079&_rerunOrigin=google&_acct=C

					000050221&_version=1&_urlVersion=0&_userid=10&md5=6978691d9c52dda8248bbe48b9a6c954 http://www.waxmelters.com/Melt-Wax-Faster-with-your-Water-Jacketed-Melter-s/82.htm
PC16	Heat transfer fluids		Suspended in liquids (IIIb)		http://www.wikipatents.com/US-Patent-7377176/nano-particle-modified-fill-fluid-for-pressure-transmitters
PC17	Hydraulic fluids		Suspended in liquids (IIIb)		http://www.nanotechproject.org/inventories/consumer/search/?keywords=ink&company=0&country_origin=0&categories=0&subcategories=0&created=&modified=&search=1
PC18	Ink and toners		Suspended in liquids (IIIb)		
PC19	Intermediate				
PC20	Products such as ph-regulators, flocculants, precipitants, neutralization agents	This category covers processing aids used in the chemical industry	Suspended in liquids (IIIb)		
PC21	Laboratory chemicals		Suspended in liquids (IIIb)	Airborne (IIId)	http://www.nanotechproject.org/inventories/consumer/search/?keywords=impregnation&company=0&country_origin=0&categories=0&subcategories=0&created=&modified=&search=1
PC23	Leather tanning, dye, finishing, impregnation and care products		Suspended in liquids (IIIb)		http://www.nanotechproject.org/inventories/consumer/browse/products/5170/
PC24	Lubricants, greases, release products		Suspended in liquids (IIIb)		
PC25	Metal working fluids		Suspended in liquids (IIIb)		

PC26	Paper and board dye, finishing and impregnation products: including bleaches and other processing aids		Suspended in liquids (IIIb)		http://www.nanotechproject.org/inventories/consumer/browse/products/7108/
PC27	Plant protection products		Suspended in liquids (IIIb)		
PC28	Perfumes, fragrances		Suspended in liquids (IIIb)	Airborne (IIId)	
PC29	Pharmaceuticals		Suspended in liquids (IIIb)		
PC30	Photo-chemicals		Suspended in liquids (IIIb)		http://www.nanotechproject.org/inventories/consumer/search/?keywords=wax&company=0&country_origin=0&categories=0&subcategories=0&created=&modified=&search=1 http://www.nanotechproject.org/inventories/consumer/search/?keywords=polish&company=0&country_origin=0&categories=0&subcategories=0&created=&modified=&search=1
PC31	Polishes and wax blends		Suspended in liquids (IIIb)		http://www.sciencedirect.com/science?_ob=ArticleURL&_udi=B6TH1-4X1YCFX-6&_user=10&_coverDate=02%2F01%2F2010&_rdoc=1&_fmt=high&_orig=search&_sort=d&_docanchor=&view=c&_searchStrId=1343350524&_rerunOrigin=google&_acct=C000050221&_version=1&_urlVersion=0&_userid=10&md5=703a6346fcb098d5a9d1f4f395e5fd97 http://www.imm.ac.cn/journal/ccl/1511/151124-1342-03-0827-p3.pdf
PC32	Polymer preparations and		Suspended in	Suspended in	http://www.nanotechproject.org/inventories/consumer/browse/products/amd_athlo

	compounds		liquids (IIIb)	solid (IIIc)	n_64_fx_processor/ http://www3.interscience.wiley.com/journal/106582703/abstract?CRETRY=1&SRETRY=0
PC33	Semiconductors		Structured surface (IIa)	Suspended in liquids (IIIb)	
PC34	Textile dyes, finishing and impregnating products; including bleaches and other processing aids		Suspended in liquids (IIIb)		http://www.nanotechproject.org/inventories/consumer/search/?search=1&keywords=washing
PC35	Washing and cleaning products (including solvent based products)		Surface bound (IIIa)	Suspended in liquids (IIIb)	http://www.magneticwatersystems.com/custom-water-filters.html
PC36	Water softeners		Suspended in liquids (IIIb)	Airborne (IIId)	
PC37	Water treatment chemicals		Suspended in liquids (IIIb)		
PC38	Welding and soldering products (with flux coatings or flux cores.), flux products		Suspended in solid (IIIc)	Bulk (Ia)	
PC39	Cosmetics, personal care products		Surface bound (IIIa)	Suspended in liquids (IIIb)	
PC40	Extraction agents		Suspended in liquids (IIIb)	Airborne (IIId)	
PC0	Other (UCN codes: see last row)				
Other (use UCN codes: see last row)					

http://www.rivm.nl/en/healthanddisease/productsafety/ConsExpo.jsp

http://195.215.251.229/fmi/xsl/spin/SPIN/guide/menuguide.xsl?-db=spinguide&-lay=overview&-view#

Table 3.3 Default colors assigned to technical functions a substance may have in a chemical product (preparation*) or article

	Function	Explanation	Location of the nanoelement
1	Aerosol propellants	Compressed or liquefied gases within which substances are dissolved or suspended and expelled from a container upon discharge of the internal pressure through expansion of the gas	Suspended in liquid (IIIb); Airborne (IIId)
2	Agents adsorbing and absorbing gases or liquids	Substances used to absorb or adsorb gases or liquids: filter materials/media; molecular sieves; silica gel, etc.	Suspended in liquids (IIIb), Bulk (IIb), Surface bound (IIIa)
3	Anti-condensation agents	Substances used to avoid condensation on surfaces and in the atmosphere: anti-dim agents; condensation removers	Surface bound (IIIa)
4	Anti-freezing agents	Substances used to prevent and remove ice formation: antifreeze liquids; deicing agents	Suspended in liquids (IIIb), Airborne (IIId)
5	Anti-set off and adhe-sive agents	Substances used to prevent set-off and adhesion: spraying powder and anti-set-off additives for printing; oils and waxes for laths and shuttering; casting slip, etc.	Suspended in liquids (IIIb), Airborne (IIId)
6	Anti-static agents	Substances used to prevent or reduce the tendency to accumulate electrostatic charges: anti-static additives; substances for surface treatment against static	Surface bound (IIIa)

		electricity	
7	Binding agents	Resin or polymer-substances in coatings and adhesives	Suspended in liquids (IIIb)
8	Biocide substances		Suspended in liquids (IIIb), Airborne (IIId)
9	Bleaching agents	Substances used to whiten or decolourise materials. Not: cosmetics; photographic bleaches; optical brighteners.	Suspended in liquids (IIIb)
10a	Colouring agents, dyes		Suspended in liquids (IIIb)
10b	Colouring agents, pigments		Suspended in liquids (IIIb); Powders
11	Complexing agents	Substances used to combine with other substances (mainly metal ions) to form complexes	Suspended in liquids (IIIb), Powders
12	Conductive agents	Substances used to conduct electrical current. Sub-categories electrolytes; electrode materials.	Suspended in liquids (IIIb), Bulk (IIb), Powders
13	Corrosion inhibitors and anti-scaling agents	Substances used to prevent corrosion: corrosion inhibiting additives; rust preventives	Suspended in liquids (IIIb), Airborne (IIId)
14	Dust binding agents	Substances used to control finely divided solid particles of powdered or ground materials to reduce their discharge into	Suspended in liquids (IIIb), Powders

		the air		
15	Explosives	Suspended in liquids (IIIb)		
16	Fertilisers	Suspended in liquids (IIIb); Powder		
17	Fillers	Relatively inert, and normally non-fibrous, finely divided substances added to elastomers, plastics, paints, ceramics, etc., usually to extend volume	Suspended in liquids (IIIb); Suspended in a solid (IIIc)	
18	Fixing agents	Substances used to interact with a dye on fibres to improve fastness	Suspended in liquids (IIIb)	
19	Flame retardants	Substances incorporated into, or applied to the surface of, materials to slow down or prevent combustion	Surface bound (IIIa)	
20	Flotation agents	Substances used to concentrate and obtain minerals from ores: flotation oil; flotation, depressants	Suspended in liquids (IIIb)	
21	Flux agents for casting	Substances used to promote the fusing of minerals or prevent oxide formation	Suspended in liquids (IIIb), Powders	
22	Foaming (blowing) agents	Substances used to form a foam or cellular structure in a plastic or rubber material: physically by expansion of compressed gases or vaporisation of liquid, or chemically by decomposition evolving a gas	Suspended in liquids (IIIb)	Suspended in a solid (IIIc)
23	Food/feedstuff additives		Suspended in liquids (IIIb), Powders	
24	Fuels and fuel additives		Suspended in liquids (IIIb)	
25	Heat transfer agaents		Suspended in liquids (IIIb), Powders	
26	Impregnation agents	Substances used to admix with solid materials, which retain their original form: impregnating agents for leather, paper, textile and wood. Not: flame retardants; conserving agents; biocides.	Suspended in liquids (IIIb	

27	Intermediates			
28	Laboratory chemicals	Substances used in laboratories for analytical purposes	Suspended in liquids (IIIb), Powders	
29	Lubricants and lubricant additives	Substances entrained between two surfaces and thereby used to reduce friction: oils; fats; waxes; friction reducing additives	Suspended in liquids (IIIb	
30	Odour agents	Substances used to produce, enhance or mask odour. Not: food additives; cosmetics.	Suspended in liquids (IIIb)	
31	Oxidizing agents	Substances that give up oxygen easily, remove hydrogen from other sub-stances, or accept electrons in chemical reactions, and are used for such purposes	Suspended in liquids (IIIb), Powders	Bulk (IIb)
32	Pharmaceutical substance		Suspended in liquids (IIIb)	
33	Photosensitive agents and other photo-chemicals	Substances used to create a permanent photographic image. Sub-categories: desensitisers; developers; fixing agents; photosensitive agents; sensitizers; anti-fogging agents; light stabilisers; intensifiers.	Suspended in liquids (IIIb)	
34	pH-regulating agents		Suspended in liquids (IIIb); Powders	
35	Plant protection active substance		Suspended in liquids (IIIb); Powders	
36	Plating agents and metal surface treating agents		Suspended in liquids (IIIb)	
37	Pressure transfer agents		Suspended in liquids (IIIb), Powders	Bulk (IIb)
38	Process regulators, other than polymerization or vulcanization processes	Substances used to regulate the speed of a (chemical) process, e.g. accelerators; activators; catalysts; inhibitors; siccatives; anti-siccatives; cross-linking	Suspended in liquids (IIIb), Powders	Surface bound (IIIa)

		agents; initiators; photo-initiators, etc.		
39	Process regulators, used in vulcanization or polymerization processes	Substances used to regulate the speed of a (chemical) process, e.g. accelerators; activators; catalysts; inhibitors; siccatives; anti-siccatives; Cross-linking agents; initiators; photo-initiators, etc.	Suspended in liquids (IIIb), Powders	Surface bound (IIIa)
40	Processing aid, not otherwise listed			
41	Reducing agents	Substances used to remove oxygen, hydrogenate or, in general, act as electron donors in chemical reactions	Suspended in liquids (IIIb), Powders	Surface bound (IIIa)
42	Reprographic agents (Toners)	Substances used to reproduce a permanent image	Suspended in liquids (IIIb)	Bulk (Ib)
43	Semiconductors and photovoltaic agents	Substances having resistivities that are between those of insulators and metals, and are usually changeable by light, heat or electrical or magnetic field, or generate electromotive force upon the incidence of radiant energy	Suspended in liquids (IIIb)	Bulk (Ib)
44	Softeners	Substances used for softening materials to improve feel, to facilitate finishing processes or to impart flexibility or workability. Sub-categories: coalescing agents; bates (leather technology); de-vulcanising agents; emollients; swelling agents; water softeners; plasticisers.	Suspended in liquids (IIIb)	
45	Solvents	Substances used to dissolve, thin, dilute and extract: extraction agents; solvents and thinners for paints, lacquers, adhesives and other materials	Suspended in liquids (IIIb)	

46	Stabilisers	Substances used to prevent or slow down spontaneous changes in, and aging of, materials	Suspended in liquids (IIIb);	Suspended in solid (IIIc)
47	Surface active agents	Substances used to lower the surface and/or interfacial tension of liquids and promote cleaning, wetting, dispersion, etc.	Suspended in liquids (IIIb), Powders	
48	Tanning agents	Substances used for treating hides and skins	Suspended in liquids (IIIb)	
49	Viscosity adjustors	Substances used to modify the flow characteristics of other substances, or preparations, to which they are added	Suspended in liquids (IIIb); Powder	
50	Other			

Table 3.4 Default colors assigned to Article categories, no release intended (AC)

	Article categories (and non exhaustive examples) for describing the type of article in which the substance is contained during service life and waste life	Suitable TARIC chapters	Location of the nanoelement	
Categories of complex articles				
AC1	Vehicles	86-89	Suspended in solid (IIIc)	
	Examples: Trucks, passenger cars and motor cycles, bicycles, tricycles and associated transport equipment; other vehicles: Railway, aircraft, vessels, boats			
AC2	Machinery, mechanical appliances, electrical/electronic articles	84/85	Suspended in solid (IIIc)	
	Examples: Machinery and mechanical appliances; electrical and electronic articles, e.g. computers, video and audio recording, communication equipment; lamps and lightening; cameras; refrigerator, dish washer, washing machines			
AC3	Electrical batteries and accumulators	8506/07	Suspended in solid (IIIc)	Suspended in liquids (IIIb
Categories of material based articles				
AC4	Stone, plaster, cement, glass and ceramic articles	68/69/70	Suspended in solid (IIIc)	
	Examples: Glass and ceramic article: e.g. dinner ware, drinking glasses, pots, pans, food storage containers; construction and isolation articles; natural or artificial abrasive powder or grain, on a base of textile material, of paper, of paperboard or of other materials			
AC5	Fabrics, textiles and apparel	50-63, 94/95	Surface bound (IIIa)	
	Examples: Clothing, bedding, mattress, curtains, upholstery, carpeting/flooring, car seats, textile toys			
AC6	Leather articles	41-42, 64, 94	Surface bound (IIIa)	Suspended in solid (IIIc)
	Examples: Cutlery, cooking utensils, pots, pans, jewellery, toys, furniture, construction articles			
AC8	Paper articles	48-49	Surface bound (IIIa)	Suspended in solid (IIIc)

	Examples: Paper articles: tissue, towels, disposable dinnerware, nappies, feminine hygiene products, adult incontinence products; paper articles for writing, office pa-per; printed paper articles: e.g. newspapers, books, magazines, printed photo-graphs; wallpaper			
AC10	Rubber articles	40, 64, 95	Surface bound (IIIa)	Suspended in solid (IIIc)
	Examples: Tyres, flooring, gloves, footwear, toys			
AC11	Wood articles	44, 94/95	Surface bound (IIIa)	Suspended in solid (IIIc)
	Examples: Flooring, walls, furniture, toys, construction articles			
AC13	Plastic articles	39, 94/95, 85/86	Surface bound (IIIa)	Suspended in solid (IIIc)
	Examples: Plastic dinner ware, food storage, food packaging, baby bottles; flooring, toys, furniture, small plastic articles of daily use e.g. ball pen, PC, mobile phone construction articles			
Other (use TARIC codes: see last row)				
http://ec.europa.eu/taxation_customs/dds/tarhome_en.htm				

Please note: This list is not complete with regard to uses potentially to be described under REACH. Describe other uses as appropriate

Table 3.5 Default colors assigned to Use descriptor for articles with intended release of substances Descriptor based on an indicative list of examples

AC30	Other articles with intended release of substances, please specify26
AC31	Scented clothes
AC32	Scented eraser
AC33	*Entry has been removed after the REACH CA meeting in March 2008*
AC34	Scented Toys
AC35	Scented paper articles
AC36	Scented CD
AC38	Packaging material for metal parts, releasing grease/corrosion inhibitors

Table 3.6 Default colors assigned to Description for Environmental Release Categories (ERC)

ERC	Name	Description	Lifecycle Stage	Level of con-tainment	Intended technical fate of substance	Dispersion of emission sources	Indoor/ outdoor	Release promotion during service life	Location of nanoele ment	Comments
1	Manufa cture of substan ces	Manufacture of organic and inorganic substances in chemical, petrochemical, primary metals and minerals industry including intermediates, monomers using continuous processes or batch processes applying dedicated or multi-purpose equipment, either technically controlled or operated by manual interventions	Manufact ure	Open-closed		Industrial	Indoor	n.a	Suspend ed in liquids (IIIb); Airborne (IIId)	Open-closed indoor industrial manufacturin g of substances might results in environment al exposure
2	Formula tion of prepara tions*	Mixing and blending of substances into (chemical) preparations in all types of formulating	Formulat ion	Open-closed	Not included into matrix	Industrial	Indoor	n.a.	Suspend ed in liquids (IIIb)	Open-closed indoor formulation not included into matrix

		industries, such as paints and do-it-yourself products, pigment paste, fuels, household products (cleaning products), lubricants, etc.								might result in environmental exposure
3	Formulation in materials	Mixing or blending of substances which will be physically or chemically bound into or onto a matrix (material) such as plastics additives in master batches or plastic compounds. For instance a plasticizers or stabilizers in PVC master-batches or products, crystal growth regulator in photographic films, etc.	Formulation	Open-closed	Inclusion into/onto matrix	Industrial	Indoor	n.a.	Surface bound (IIIa); Suspended in solids (IIIc)	
4	Industrial use of processing aids	Industrial use of processing aids in continuous processes or batch processes	End use	Open-closed	Processing aid	Industrial	Indoor	n.a.		

	in processes and products, not becoming part of articles	applying dedicated or multi-purpose equipment, either technically controlled or operated by manual interventions. For example, solvents used in chemical reactions or the 'use' of solvents during the application of paints, lubricants in metal working fluids, anti-set off agents in polymer moulding/casting.								
5	Industrial use resulting in inclusion into or onto a matrix	Industrial use of substances as such or in preparations (non-processing aids), which will be physically or chemically bound into or onto a matrix (material) such as binding agent in paints and coatings or adhesives, dyes in	End use	Open-closed	Inclusion into/onto matrix	Industrial	Indoor	n.a.	Surface bound (IIIa); Suspended in solids (IIIc)	

		textile fabrics and leather products, metals in coatings applied through plating and galvanizing processes. The category covers substances in articles with a particular function and also substances remaining in the article after having been used as processing aid in an earlier life cycle stage (e.g. heat stabilisers in plastic processing).								
6a	Industrial use resulting in manufacture of another substance (use of interme	Use of intermediates in primarily the chemical industry using continuous processes or batch processes applying dedicated or multi-purpose equipment, either technically controlled or operated by manual	End use	Open-closed	Intermediate	Industrial	Indoor	n.a.		

	diates)	interventions, for the synthesis (manufacture) of other substances. For instance the use of chemical building blocks (feedstock) in the synthesis of agrochemicals, pharmaceuticals, monomers, etc.								
6b	Industrial use of reactive processing aids	Industrial use of reactive processing aids in continuous processes or batch processes applying dedicated or multi-purpose equipment, either technically controlled or operated by manual interventions. For example the use of bleaching agents in the paper industry.	End use	Open-closed	Reactive processing aid	Industrial	Indoor	n.a.	Suspended in liquids (IIIb)	
6c	Industrial use of monom	Industrial use of monomers in the production of	End use	Open-closed	Monomers for polymers	Industrial	Indoor	n.a.	Suspended in solids	

	ers for manufacture of thermo plastics	polymers, plastics (thermoplastics), polymerization processes. For example the use of vinyl chloride monomer in the production of PVC.							(IIIc)	
6d	Industrial use of process regulators for polymerisation processes in production of resins, rubbers, polymers	Industrial use of chemicals (cross-linking agents, curing agents) in the production of thermosets and rubbers, polymer processing. For instance the use of styrene in polyester production or vulcanization agents in the production of rubbers.	End use	Open-closed	Monomers for rubbers or thermosets	Industrial	Indoor	n.a.	Suspended in solids (IIIc)	
7	Industrial use of substances in closed systems	Industrial use of substances in closed systems. Use in closed equipment, such as the use of liquids in hydraulic	End use	Closed system	Processing aid	Industrial	Indoor	n.a.	Suspended in liquids (IIIb)	The description of ERC7 states that "low

		systems, cooling liquids in refrigerators and lubricants in engines and dielectric fluids in electric transformers and oil in heat exchangers. No intended contact between functional fluids and products foreseen, and thus low emissions via waste water and waste air to be expected.								emissions via waste water and waste air to be expected.”
8a	Wide dispersive indoor use of processing aids in open systems	Indoor use of processing aids by the public at large or professional use. Use (usually) results in direct release into the environment/sewage system, for example, detergents in fabric washing, machine wash liquids and lavatory cleaners, automotive and bicycle care products (polishes, lubricants, deicers), solvents in paints and adhesives	End use	Open-closed	Processing aid	Wide dispersive	Indoor	n.a.	Suspended in liquids (IIIb)	Open-closed wide dispersive use and the ERC8a description states that: “Use (usually) results in direct release into the environment /sewage system,…”

		or fragrances and aerosol propellants in air fresheners.								
8b	Wide dispersive indoor use of reactive substances in open systems	Indoor use of reactive substances by the public at large or professional use. Use (usually) results in direct release into the environment, for example, sodium hypochlorite in lavatory cleaners, bleaching agents in fabric washing products, hydrogen peroxide in dental care products.	End use	Open-closed	Reaction on use	Wide dispersive	Indoor	n.a.	Suspended in liquids (IIIb)	Open-closed wide dispersive use and the ERC8b description states that "Use (usually) results in direct release into the environment …"
8c	Wide dispersive indoor use resulting in inclusion into or onto a matrix	Indoor use of substances (non-processing aids) by the public at large or professional use, which will be physically or chemically bound into or onto a matrix (material) such as binding agent in paints and coatings or adhesives, dyeing of textile fabrics.	End use	Open-closed	Inclusion into/onto matrix	Wide dispersive	Indoor	n.a.	Surface bound (IIIa); Suspended in solids (IIIc)	Open-closed wide dispersive onto or including into a matrix which indicates limited exposure on the environment

8d	Wide dispersive outdoor use of processing aids in open systems	Outdoor use of processing aids by the public at large or professional use. Use (usually) results in direct release into the environment, for example, automotive and bicycle care products (polishes, lubricants, deicers, detergents), solvents in paints and adhesives.	End use	Open-closed	Processing aid	Wide dispersive	Outdoor	n.a.	Suspended in liquids (IIIb)	Open-closed wide dispersive use and the ERC8b description states that "Use (usually) results in direct release into the environment …"
8e	Wide dispersive outdoor use of reactive substances in open systems	Outdoor use of reactive substances by the public at large or professional use. Use (usually) results in direct release into the environment, for example, the use of sodium hypochlorite or hydrogen peroxide for surface cleaning (building materials)	End use	Open-closed	Reaction on use	Wide dispersive	Outdoor	n.a.	Suspended in liquids (IIIb)	Open-closed wide dispersive use and the ERC8b description states that "Use (usually) results in direct release into the environment …"

8f	Wide dispersive outdoor use resulting in inclusion into or onto a matrix	Outdoor use of substances (non-processing aids) by the public at large or professional use, which will be physically or chemically bound into or onto a matrix (material) such as binding agent in paints and coatings or adhesives.	End use	Open-closed	Inclusion into/onto matrix	Wide dispersive	Outdoor	n.a.	Surface bound (IIIa); Suspended in solids (IIIc)	Open-closed wide dispersive onto or including into a matrix which indicates limited exposure on the environment
9a	Wide dispersive indoor use of substances in closed systems	Indoor use of substances by the public at large or professional (small scale) use in closed systems. Use in closed equipment, such as the use of cooling liquids in refrigerators, oil-based electric heaters.	End use	Closed systems	Processing aid	Wide dispersive	Indoor	n.a.	Suspended in liquids (IIIb)	Indoor use in closed systems indicates the possibility of environmental exposure whereas the widely disperse nature of the use indicates the possibility of environmental potential

9b	Wide dispersive outdoor use of substances in closed systems	Outdoor use of substances by the public at large or professional (small scale) use in closed systems. Use in closed equipment, such as the use of hydraulic liquids in automotive suspension, lubricants in motor oil and break fluids in automotive brake systems.	End use	Closed systems	Processing aid	Wide dispersive	Outdoor	n.a.	Suspended in liquids (IIIb)	Outdoor and widely disperse use by the public at large indicates the possibility of environmental exposure use in a closed equipment indicates the possibility of environmental potential
10a	Wide dispersive outdoor use of long-life articles and materials with low release	Low release of substances included into or onto articles and materials during their service life in outdoor use, such as metal, wooden and plastic construction and building materials (gutters, drains, frames, etc.)	Service life	Open	Inclusion into/onto matrix	Wide dispersive	Outdoor	Low	Surface bound (IIIa); Suspended in solids (IIIc)	Open outdoor wide dispersive onto or including into a matrix indicates some, but limited exposure to the environment

10b	Wide dispersive outdoor use of long-life articles and materials with high or intended release (including abrasive processing)	Substances included into or onto articles and materials with high or intended release during their service life from outdoor use. Such as tyres, treated wooden products, treated textile and fabric like sun blinds and parasols and furniture, zinc anodes in commercial shipping and pleasure craft, and brake pads in trucks or cars. This also includes releases from the article matrix as a result of processing by workers. These are processes typically related to PROC 21, 24, 25, for example: Sanding of buildings (bridges, facades) or vehicles (ships).	Service life	Open	Inclusion into/onto matrix Removing from matrix	Wide dispersive	Outdoor	High	Surface bound (IIIa); Suspended in solids (IIIc)	Open outdoor wide dispersive onto or including into a matrix followed by "Removing from matrix" indicates high levels of exposure to the environment
11a	Wide dispersive indoor use of	Low release of substances included into or onto articles and materials during their service life from	Service life	Open	Inclusion into/onto matrix	Wide dispersive	Indoor	Low	Surface bound (IIIa); Suspend	Open indoor wide dispersive onto or

	long-life articles and materials with low release	indoor use. For example, flooring, furniture, toys, construction materials, curtains, footwear, leather products, paper and cardboard products (magazines, books, news paper and packaging paper), electronic equipment (casing).							ed in solids (IIIc)	including into a matrix indicates some, but limited exposure to the environment
11b	Wide dispersive indoor use of long-life articles and materials with high or intended release (including abrasive processing)	Substances included into or onto articles and materials with high or intended release during their service life from indoor use. For example: release from fabrics, textiles (clothing, floor rugs) during washing. This also includes releases from the article matrix as a result of processing by workers. These are processes typically related to PROC 21, 24, 25. For example removal of indoor paints.	Service life	Open	Inclusion into/onto matrix Removing from matrix	Wide dispersive	Indoor	High	Surface bound (IIIa); Suspended in solids (IIIc)	Open indoor wide dispersive onto or including into a matrix followed by "Removing from matrix" indicates high levels of exposure to the environment

12a	Industrial processing of articles with abrasive techniques (low release)	Substances included into or onto articles and materials are released (intended or not) from the article matrix as a result of processing by workers. These processes are typically related to PROC 21, 24, 25. Processes where the removal of material is intended, but the expected release remains low, include for example: cutting of textile, cutting, machining or grinding of metal or polymers in engineering industries.	Service life	Open-closed	Losses from matrix during article processing	Industrial	Indoor	Low	Surface bound (IIIa); Suspended in solids (IIIc)	Open-closed indoor wide dispersive onto or including into a matrix indicates some, but limited exposure to the environment
12b	Industrial processing of articles with abrasive techniques (high release)	Substances included into or onto articles and materials are released (intended or not) from/with the article matrix as a result of processing by workers. These processes are typically related to PROC 21, 24, 25.	Service life	Open-closed	Losses with matrix during article processing	Industrial	Indoor	High	Surface bound (IIIa); Suspended in solids (IIIc)	Open-closed indoor wide dispersive onto or including into a matrix followed by "Losses with matrix during article

		Processes where the removal of material is intended, and high amounts of dust may be expected, includes for example: sanding operations or paint stripping by shot-blasting.								processing" indicates high levels of exposure to the environment

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Preface

The Danish Environmental Protection Agency (DEPA) has previously initiated projects which have highlighted the nanomaterials that can be found in products on the Danish market (Consumer Project No. 81), and the nanomaterials used in the Danish industry (Environmental Project No. 1206).

As a follow-up on these reports, the DEPA identified a need to try to develop a concept that can provide support to companies and regulators in regard to assessing, ranking and communicating what they know about the risks of nanomaterials in specific uses in products.

DEPA has therefore initiated this project in order to examine the possibilities for developing such a conceptual framework for screening of potential environmental and health risks for nanomaterials used in products. DEPA contracted with DTU Environment in collaboration with the National Research Centre for the Working Environment to carry out this task.

The current project is one of the initiatives under the national action plan for Chemicals which also includes a survey on basic knowledge about exposure and potential environmental and health risks for selected nanomaterials (Environmental Project) and on carbon nanotubes (Environmental Project).

The study has been guided by a steering group consisting of Flemming Ingerslev and Poul Bo Larsen (Danish Environmental Protection Agency), Poul-Erik Andersen (The Danish Working Environment Authority), Ulla Vogel (DTU Food/ National Research Centre for the Working Environment), and Stig I. Olsen (DTU Management)

This report was prepared by Steffen Foss Hansen (DTU Environment), Anders Baun (DTU Environment), and Keld Alstrup Jensen (National Research Centre for the Working Environment) during a period from January 2010 to May 2011.

Please note that the publication of this report does not signify that the content necessarily reflects the view of the Danish EPA.

Danish Environmental Protection Agency, November 2011

Dansk Sammenfatning

Nanomaterialer bliver anvendt i et hastigt stigende antal produkter til gavn for såvel virksomheder som private forbrugere. Antallet af mulige nanomaterialer er ubegrænsede og de forbedrede materialeegenskaber, der opnås på grund af nano-størrelsen muliggør brug i vidt forskellige produkter. I løbet af det sidste årti er der, samtidigt med udviklingen af nanoteknologien, sat fokus på de mulige miljø- og sundhedsskadelige egenskaber af nogle typer af nanomaterialer.

På den baggrund har Miljøstyrelsen identificeret et behov for at undersøge mulighederne for at udvikle et nyt vurderings-koncept, som kan yde støtte til virksomheder og myndigheder i forbindelse med vurdering, rangordning og formidling viden om af hvad de ved om mulige risici af nanomaterialer i specifikke produktanvendelser. Risiko forstås i denne sammenhæng som en kombination af 1) muligheden for eksponering af nanomaterialet gennem den specifikke anvendelse og 2) muligheden for at der kan ske en negativ påvirkning af menneskelig sundhed eller miljøets organismer.

Gennem dette projekt har DTU Miljø og Det Nationale Forskningscenter for Arbejdsmiljø igangsat udviklingen af et konceptuelt screeningsværktøj, NanoRiskCat (NRC), med det formål at muliggøre en identifikation, kategorisering og rangordning af eksponering og effekter af nanomaterialer, der anvendes i forbrugerprodukter. NanoRiskCat er baseret på data til rådighed i peer-reviewed videnskabelige litteratur og andre former for reguleringsmæssigt relevante kilder.

Fokus for NRC er på anvendelse og udsættelse for nanomaterialer i forbindelse med professionelle brugere, private forbrugere, samt miljømæssige udledning. Det er håbet, at NanoRiskCat kan og vil hjælpe producenter, brugere, regulerende myndigheder, og andre interessenter med at vurdere, kategorisere, rangordne og kommunikere den nuværende viden om potentialet for eksponering og effekter af nanomaterialer. Dette er forsøgt gjort gennem en generisk velstruktureret skabelon, hvor de specifikke anvendelser af et givet nanomateriale rapporteres og vurderes. Helt konkret gøres dette i NRC ved at fastsætte detaljerede retningslinjer for kortlægning og indberetning af:

1. Eksponeringspotentiale for professionelle slutbrugere
2. Eksponeringspotentiale for forbrugerne
3. Eksponeringspotentiale for miljøet
4. En foreløbig farlighedsevaluering for mennesker
5. En foreløbig farlighedsevaluering for miljøet

En generisk skabelon for kortlægning og rapportering af disse fem punkter for en bestemt anvendelse af et nanomateriale er udviklet og kan findes i bilag 1 til denne rapport.

Resultatet af en produkt-screening med NanoRiskCat kommunikeres i form af: en kort titel, der beskriver brugen af nanomateriale og en farvekode, der består af fem punkter (f.eks. ●●●|●●). De første tre farvede prikker henviser altid til den potentielle eksponering af professionelle brugere, forbrugere og miljøet i den pågældende rækkefølge, mens de sidste to farvede prikker altid henviser til alvorligheden af de mulige fareegenskaber for henholdsvis mennesker og miljø. Farverne specificerer om den angivne eksponering og de angivne effekter vurderes til at være høj (rød), medium (gul), lav (grøn) eller ukendt (grå).

Farvekodningen af de første tre prikker, der repræsenterer eksponeringspotentialet, er baseret på de generiske proces- og produktkategorier der anvendes ved opbygning og beskrivelse af eksponeingsscenarier i REACH og som er angivet i de relevante guidance dokumenter det Europæiske Kemikalieagentur (ECHA) har udgivet[1]. Hver proceskategori- og produktkategori har i dette projekt fået tildelt en farvekode (●,●,● eller ●) baseret på 1) placeringen af nanomaterialet (bulk, overflade, væske, luftbåret, osv.) og 2) en vurdering af nanomaterialets eksponeringspotentiale baseret på den beskrivelse af de enkelte processer, produktkategorier, tekniske funktioner, artikler og miljømæssige frigivelseskategorier, som forefindes i REACH vejledningen.

Ved farvekodningen af fjerde prik, som repræsenterer de potentielle sundhedsfarer i forbindelse med anvendelsen af en given nanomateriale, bør følgende indikatorer overvejes:

1. Opfylder ***nanomaterialet*** HARN[2]-paradigmet?

2. Er ***bulk-formen*** af nanomaterialet kendt for at forårsage eller kunne medføre alvorlige skadelige effekter, dvs. er bulk formen klassificeret i kategori 1 eller 2 i henhold til CLP[3] med hensyn til en eller flere alvorlige sundhedsmæssige effekter såsom fx mutagenicitet, kræft eller reproduktionstoksicitet?

3. Er ***bulk-formen*** af nanomaterialet klassificeret for andre, mindre alvorlige sundhedsmæssige effekter i henhold til CLP?

4. Er det specifikke ***nanomateriale*** kendt for at være akut giftigt?

5. Er der tegn på, at ***nanomaterialet*** kan forårsage skadelige effekter såsom genotoksicitet, mutagenicitet, kræft, luftvejs- og hjertekarsygdomme,

[1] ECHA 2010 Guidance on information requirements and chemical safety assessment Chapter R.12: Use descriptor system Version 2. Tilgængelig: http://guidance.echa.europa.eu/docs/guidance_document/information_requirements_r12_en.pdf (Besøgt: 25-11-2011)

[2] HARN refererer til High Aspect Ratio Nanopartikler. For at nanopartikler opfylder HARN skal nanopartiklerne have en længde/diameter aspect ratio større end 10 til 1. Desuden kræves det, at: 1) Diameteren af fibrene skal være tynd nok til at passere cilierede luftveje, 2) længden skal være lang nok til at indlede begyndelsen af fx frustrerede fagocytose og anden inflammatoriske respons, og 3) de nanomaterialer skal være biopersistent (Tran et al 2008).

[3] Europa-Parlamentets og Rådets Forordning (EF) Nr. 1272/2008 af 16. december 2008 om klassificering, mærkning og emballering af stoffer og blandinger og om ændring og ophævelse af direktiv 67/548/EØF og 1999/45/EF og om ændring af forordning (EF) nr. 1907/2006

neurotoksiske eller reproduktionsskadelige effekter i mennesker og/ eller laboratoriedyr, eller er der dokumenteret en organspecifik ophobning?

De CLP klassificeringer, der allerede findes på bulk formen af materialet med hensyn til menneskelig sundhed bruges i NanoRiskCat som udgangspunkt for at etablere et minimum niveau for den toksikologiske profil af nanoformen. Principielt antages det, at oplysninger om bulk formen af materialet kan anvendes under den antagelse, at de toksikologiske og økotoksikologiske virkninger af nanomatetialet er lig med eller mere udtalt / alvorlig i forhold til bulk formen. Således kan fareoplysninger om bulk formen af materialet danne grundlag for fastlæggelsen af det laveste bekymringsniveau der bør indtages med hensyn til nanomaterialet.

Miljøfarelighedsvurderingen ved anvendelsen af et givent nanomateriale (prik fem) bør omfatte overvejelser om hvorvidt nanomaterialet er:

1. Farligt for organismer i miljøet?
2. Persistent?
3. Bioakkumulerende?
4. Fører til irreversible skader på miljøet (fx økosystem virkninger)?
5. Mobilt?
6. Nyt eller unikt?

Det er vigtigt at bemærke, at NanoRiskCat beskriver en trinvis proces i den forstand, at når en farvekode er blevet givet afsluttes processen. Dvs. hvis der fx er nok information til at give en rød farvekode pga. CLP klassificeringen af bulk formen af materialet så stopper processen.

For at hjælpe brugerne af NRC med at kommunikere den videnskabelige begrundelse for tildelingen af en farvekodning for sundheds- og miljøfarekategoriseringen, er en række standardsætninger blevet udviklet. Disse sætninger er beregnet til at afspejle primært om kategoriseringen er baseret på ***in vivo*** eller ***in vitro*** undersøgelser og med hensyn til hvilke effekter. Afhængigt til den endelige sundheds- og miljøfarekategorisering, skal brugeren af NRC vælge den af disse standardsætninger, der bedst afspejler det videnskabelige grundlag for at tildelte farvekoden.

For at illustrere anvendeligheden af NanoRiskCat er to eksempler blevet gennemført. Det ene er for C60-fullerener anvendt i et smøremiddel, mens det anden er nanoTiO_2 anvendt i solcreme. Disse to eksempler, som er udvalgt til brug for udviklingen af konceptet, men de er også medtaget i den aktuelle rapport for at at belyse mulighederne for at anvende NanoRiskCat. NanoRiskCat-koden for C60 i smøremidlet er ●●●|●● eftersom eksponeringspotentialet vurderes at være højt for professionelle slutbrugere, forbrugere og miljøet. Den potentielle sundhedsfare vurderes til at være medium (dvs. gul) baseret på ***in vitro*** data, der indikerer, at der er mindst én sundhedsskadelig effekt associeret med C60, mens den potentielle miljøfare er vurderet til at være høj (dvs. rød) baseret på flere studier, der indikerer at C60 kan forårsage letale og subletale effekter på fisk og krebsdyr ved koncentrationer < 10 mg/l. For TiO_2 i solcreme var NanoRiskCat koden ●●●|●●, da eksponeringspotentialet vurderes at være højt (dvs. rød) for

res at være højt (dvs. rød) for professionelle slutburgere, forbrugere og miljøet. Potentialet for sundhedsfarlighed af TiO_2 vurderes til at være højt (dvs. rød) baseret på ***in vitro*** data, som tyder på at nanoformen af TiO2 forårsager mindst en sundhedsskadelig effekt. På miljø-effektsiden, blev potentialet for TiO_2 også vurderet som højt, på basis af et konkret studie med dafnier, hvor den 50% af dyrene døde ved eksponering af 2 mg/L (LC_{50}) og dermed er værdien under afskæringsværdien på 10 mg/l anvendt i NanoRiskCat.

Det er vigtigt at understrege, at NanoRiskCat ikke skal ses som en mærkningsordning, men at NanoRiskCat alene skal bruges til at udføre en evaluering af et nanomateriale under de fysiske forhold hvori det forekommer i produktet. NanoRiskCat vurderer således ikke eksponering og effekter fra de øvrige ingredienser, bestanddele og urenheder i produktet, og der tages heller ikke hensyn til den konkrete indholdsmængde eller koncentration af nanomaterialet i produktet. Således er NanoRiskCat rettet mod brugen af generiske anvendelsesbeskrivelser og scenarier som for eksempel er beskrevet i de processer, produktkategorier, osv., der anvendes i REACH vejledningen. En NanoRiskCat farvekode er således anvendelsesspecifik, og en farvekode for én anvendelse kan dermed ikke overføres til en anden. Ligeledes vil NanoRiskCat farvekoder i sig selv ikke kunne bruges til generelle vurderinger sikkerheden af nanomaterialer som et hele. En væsentlig styrke ved NanoRiskCat er, at det kan bruges, selv i tilfælde, hvor manglen på data er fremtrædende og hæmmer gennemførelsen af traditionelle risikovurderingsprocedurer. En anden styrke er, at NanoRiskCat hjælper brugerne med at sortere i den litteratur, der med stigende hastighed bliver publiceret indenfor nano(øko)toksikologi. En tredje fordel ved NanoRiskCat er at resultaterne let kan kommunikeres med andre interesserede parter.

En væsentlig svaghed ved NanoRiskCat er, at mange af de afskæringsværdier, der anvendes primært i de miljømæssige farevurderinger er baseret på en masse-afhængig dosis (altså f.eks. mg/l), vel vidende om at der løbende foregår en diskussion af hvilket dosis-mål, der bedst kan bruges til effekt-beskrivelse i nano(øko)toksikologi. Derudover er den proces, hvorved farvekoden er tildelt i forbindelse med sundhedsfarevurderingen af nanoformen af et bestemt materiale primært baseret på videnskabelige ekspertvurderinger og en mere sammenfattende vurdering af evidensen for mutagenicitet, carcinogenicitet, respiratorisk toksicitet, osv. Da ekspertvurderinger af den selvsamme datagrundlag kan variere, kan såvel konklusionen som den deraf følgende farvekodningen ligeledes variere fra bruger til bruger. Det er imidlertid ikke muligt at give klare retningslinjer på dette tidspunkt for, hvordan man gennemfører en mere holistisk vurdering af de menneskelige og miljømæssige fare forbundet med nanoformen af et bestemt materiale. ***Det helt afgørende i den forbindelse er at brugerne af NRC forklarer hvilket litteratur de har identificeret som relevant og argumenterer for hvordan de fortolker de reporterede resultater og tildeler diverse farvekoder.***

Selvom NanoRiskCat er designet til at hjælpe brugere med at identificere, kategorisere, rangordne og kommunikere den nuværende viden om de nanomaterialer som de anvender, er det vigtigt at understrege at NRC i sig selv ikke fører direkte til en beslutning. Derimod giver NRC et mere kvalificeret grundlag for at tage en beslutning ved at medtage en række indikatorer som samlet set afgør om eksponering er sandsynlige (eller usandsynlig) og om nanomaterialet kan have problematiske, skadelige egenskaber.

De beslutninger, der kan efterfølge brugen af NanoRiskCat vil være interessent-afhængige. Regulerende myndigheder kunne fx bruge NRC til på screeningsbasis at udpege anvendelser, hvor risikohåndteringsmæssige foranstaltninger kan overvejes nøjere, fx udarbejdelse af retningslinjer for kontrollerede anvendelser eller evt. at undersøge mulighederne for at indføre forbud eller anvendelsesbegrænsninger eller pege på hvor der savnes viden. Virksomheder kan bruge NanoRiskCat til at kommunikere, hvad de ved om virkningerne af de nanomaterialer, de bruger, hvorefter de ligeledes kan vurdere behovet for at udvikle retningslinjer for sikker brug. Det kunne fx. være ved at ændre på formuleringen eller anvendelsen af produktet eller ved at designe mere sikre nanomaterialer. Ligeledes er det en mulighed at udarbejde retningslinjer til professionelle slutbrugere og forbrugere om sikker anvendelse af nanomaterialer. Hvis virksomheder eller andre gør deres NRC profiler offentligt tilgængelig kan forbrugere endvidere bruge NanoRiskCat til at foretage en foreløbig vurdering af en række nano-baserede produkter. Endelig, kan NRC bruges til at øge vidensdelingen om eksponeringen og effekten nanomaterialer og NanoRiskCat kan bidrage til en uafhængig vurdering og indgå i en informeret dialog om nanorisiko mellem forskere, forbrugere, virksomheder og myndigheder.

Eftersom beslutninger, der kan følge af brugen af NanoRiskCat er interessent-afhængige, er det vigtigt at understrege, at farvekoderne opnået i NanoRiskCat ikke bør ses som en absolut kategorisering. Det bør snarere fungere som et skridt i en iterativ proces, hvor interessenterne i risiko-relaterede spørgsmål kan nå frem til en fælles forståelse af potentialet for eksponering og effekter af nanomaterialer i bestemte produkter. Det er vigtigt at understrege, at det ikke har været muligt inden for rammerne af dette projekt at foretage en yderligere validering af NRC konceptet. For at opnå et mere færdigt værktøj, anses det derfor for nødvendigt at foretage yderligere validering af konceptet, herunder udføre flere forskellige casestudier, og herigennem eventuelt tilpasse processerne og de kriterier der benyttes i NRC for at opnå et screeningsværktøj, der er så bredt anvendeligt, praktisk og informativt som muligt.

Executive Summary

Nanomaterials are being used in a rapidly increasing number of products available for industries and private consumers. The number of nanomaterials that can be manufactured using nanotechnologies is immense and the improved material properties enable use in multiple different products. During the last decade more and more evidence has emerged in the scientific literature suggesting that some nanomaterials may have hazardous properties.

With this background, the Danish Environmental Protection Agency has identified a need for developing a new concept that can provide support to companies and regulators in regard to assessing, ranking and communicating what they know about the risks of nanomaterials in specific product uses. In this case, risk should be defined as a combination of the likelihood of exposure and adverse effects, i.e. any chance of an adverse outcome to human health, the quality of life, or the quality of environment.

Through this project, DTU Environment and the National Research Centre for the Working Environment have initiated the development of a screening tool, NanoRiskCat (NRC), that is able to identify, categorize and rank exposures and effects of nanomaterials used in consumer products based on data available in the peer-reviewed scientific literature and other regulatory relevant sources of information and data. The primary focus was on nanomaterials relevant for professional end-users and consumers as, as well as nanomaterials released into the environment.

The wider goal of NanoRiskCat is to help manufacturers, down-stream end-users, regulators and other stakeholders to evaluate, rank and communicate the potential for exposure and effects through a tiered approach in which the specific applications of a given nanomaterial are evaluated. This is done by providing detailed guidance on mapping and reporting of the:

1. Exposure potential for professional end-users
2. Exposure potential for consumers
3. Exposure potential for the environment
4. A preliminary hazard evaluation for humans
5. A preliminary hazard evaluation for the environment

A generic template for mapping and reporting these five aspects for a specific application of a given nanomaterial has been developed and can be found in Appendix 1 of this report.

In its simplest form, the final outcome of using NanoRiskCat for a nanomaterial in a given application will be communicated in the form of a short title describing the use of the nanomaterial (e.g. MeO in ship paint) and a five-color coded dots (e.g.,), where the first three dots always refer to potential exposure of professional end-users, consumers and the environment in that

sequence and the last two colors always refer to the hazard potential for humans and the environment. The colors signify whether the indications of exposures or effects separately are high (red), medium (yellow), low (green), or unknown (grey).

The color-coding of the dots representing the exposure potential (dost numbers one to three) is based on the generic use descriptor system established by the European Chemicals Agency (ECHA) in the current REACH Guidance on information requirements and chemical safety assessment Appendix R.124. For each use category, a color code (●, ●, ● or ●) has been assigned based on 1) the location of the nanomaterial (bulk, on the surface, liquid or airborne) and 2) a judgment of the potential for nanomaterial exposure based on the description and explanation of each process, product category, technical function, article and environmental release category provided in the REACH Guidance.

When assigning a color to the dot representing potential human health hazards (dot number four) related to the specific application of a given nanomaterial the following indicators/qualifiers should be considered:

1. Does the ***nanomaterial*** fulfil the HARN[5] paradigm?

2. Is the ***bulk form*** of the nanomaterial known to cause or may cause serious damaging effects, i.e. is the bulk form classified according to the CLP[6] with regard to one or more serious health hazards such as germ cell mutagenicity, carcinogenicity or reproductive toxicity in category 1A, 1B or 2?

3. Is the ***bulk form*** of the nanomaterial classified for other less severe adverse effects according to the CLP such as skin corrosion/irritation category 2 and specific target organ toxicity-single exposure category 3?

4. Is the specific ***nanomaterial*** known to be acute toxic?

5. Are there indications that the ***nanomaterial*** causes genotoxic, mutagenic, carcinogenic, respiratory, cardiovascular, neurotoxic or reproductive effects in humans and/or laboratory animals or has organ-specific accumulation been documented?

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[4] ECHA 2010 Guidance on information requirements and chemical safety assessment Chapter R.12: Use descriptor system Version 2. Available: http://guidance.echa.europa.eu/docs/guidance_document/information_requirements_r12_en.pdf (Accessed 25-04-2011)

[5] HARN refers to High Aspect Ratio Nanoparticles indicating that the nanoparticles have a length to diameter aspect ratio greater than 10 to 1. Furthermore, it is required that: 1) The diameter of the fibres must be thin enough pass ciliated airways; 2) the length must be long enough to initiate the onset of e.g. frustrated phagocytosis and other inflammatory pathways; and 3) the nanomaterials must be biopersistent (Tran ***et al.*** 2008).

[6] Regulation (EC) No 1272/2008 of the European Parliament and of the Council of 16 December 2008 on classification, labelling and packaging of substances and mixtures, amending and repealing Directives 67/548/EEC and 1999/45/EC, and amending Regulation (EC) No 1907/2006

The human hazards information on the bulk form of the material may be used as a starting point in order to describe a possible minimum level of concern in regard to the toxicological profile for the nanomaterial. A guiding principle is that information about the bulk form of the material can be used under the assumption that any toxicological and ecotoxicological effects of the nanomaterial are equal to or larger than those reported on for the bulk material. Thus hazard data on the bulk material forms the basis of the lowest level of concern with regard to the nanomaterial.

In NRC, indications of the level of environmental effects (dot number five) should include considerations of whether the ***nanomaterial*** in question is reported to be:

1. Hazardous to environmental species?
2. Persistent?
3. Bioaccumulative?
4. Leading to potentially irreversible harm to the environment (e.g. ecosystem effects)?
5. Readily dispersed?
6. Novel?

It is important to note that NanoRiskCat is a stepwise and tiered approach in the sense that once a color code has been triggered this finalizes the screening process.

To help communicate the scientific reasoning behind the human health and environmental hazard categorization and the assigned color code, a number of standard sentences have been included in the framework. These sentences are primarily meant to reflect whether the categorization has been reached based on ***in vivo*** or ***in vitro*** studies and in regard to which effect or endpoint. Depending to the final categorization in regard to human health and environment, the user of NRC has to select one or more of those sentences that best reflect the scientific basis for assigning the color code.

In order to illustrate the feasibility of NanoRiskCat two nanomaterials (titanium dioxide and C_{60}) were used as training sets in two different applications i.e. C_{60} used in a lubricant and TiO_2 used in sunscreen. These examples were chosen order to be used in the development of the concept but they are also included in the current report in order to illustrate the applicability of NanoRiskCat. The NanoRiskCat code of C_{60} used in a lubricant was ●●●|●● as the exposure potential is high for professional end-users, comsumers and the environment. The human hazard potential was evaluated to be medium (yellow) based on ***in vitro*** evidence indicating at least one human hazard specifically associated with C60, whereas the environmental hazard potential was evaluated to be high (red) because studies indicate that C60 may cause lethal or sublethal effects on fish and crustaceans on levels below the cut-off values set in NanoRiskCat (i.e., LC_{50} or EC_{50} values < 10 mg/l). For TiO_2 in sunscreen the NanoRiskCat code was ●●●|●● as the exposure potential is high (red) for professional end-users, comsumers and the environment. The human and environmental hazard potential was also evaluated to be high

(red) based on ***in vivo*** data of severe effects of nano-TiO_2. The potential of environmental effects was also evaluated as high on basis of one study with daphnids where LC_{50} was 2 mg/L which is under the cut-off value of the NRC concept.

It is important to underline that NanoRiskCat is not a product label and NanoRiskCat is only to be used for evaluating the nanomaterial as an ingredient under the physical conditions it occurs in the product. NanoRiskCat does not evaluate exposure and effects from the other constituents and impurities in the product nor does it take into account the specific content of nanomaterial in the product. Thus, NanoRiskCat is directed towards the generic use descriptors and scenarios, which for instance are apparent in the product categories used in REACH. Although NanoRiskCat is generic in nature and can be used on all kinds of nanomaterials and applications, the NanoRiskCat color code itself is application-specific. Thus, a NanoRiskCat color code does not in itself allow for an overall evaluation of risks associated with a given nanomaterial.

A significant strength of NanoRiskCat is that it can be used even in cases where lack of data is prominent and hampers the completion of traditional risk assessment procedures. Another is that the results of NanoRiskCat can be easily communicated to interested parties. A significant weakness of NanoRiskCat is that many of the cut-off values used primarily in the environmental hazard evaluation is based on dose-by-mass which we know is probably not valid for all nanomaterials as it is an ongoing discussion on which dose-metrics will be the best to use in nano-ecotoxicology. Furthermore, the process by which the color code is assigned to human hazards associated with the nanoform of a given material is based primarily on scientific expert judgement and a holistic assessment of the evidence of mutagenicity, carcinogenicity, respiratory toxicity, etc. As expert interpretation of scientific literature vary, so can the conclusion reached and the human hazard color code assigned to nanomaterial. It is not possible to provide clear-cut guidance and rules at this point in time for how to complete holistic evaluation of the human and environmental hazards associated with the nanoform of a given material. ***It is crucial in this context that the users of the NRC explain what literature they have identified as relevant and explain how they interpret the reported results and assign the various color codes in the NRC template provided in Appendix 1.***

The result of NRC does not lead directly to an decision in contrast to other decision-making tools available for nanomaterials, but NRC does provide a informed and structured foundation for decision-making by including a number of indicators that define whether exposure and effects are likely (or unlikely) to occur and whether the nanomaterial may have harmful properties of concern.

Decisions that could come out of using NanoRiskCat are stakeholder-dependent. Regulators could use NRC as a screening tool to identify possible uses where risk management measures may be further examined e.g. to develop guidance on controlled uses, or to evaluate whether specific restrictions would be required or to indentify data needs. Companies can use NanoRiskCat to communicate what they know about the exposures and effects of the nanomaterial they use, assess the need to develop guidance for safe uses that e.g. limit exposures by changing the product formulation or the use of the

nanoproduct or work systematically with designing safer nanomaterials. Likewise, the company could develop guidelines for professional end-users and consumers about the safe uses of their nanomaterials and products. Down-stream users (e.g. consumers) can use NanoRiskCat to make a preliminary assessment of a range of nanomaterials as a mean to select the seemingly safest material. Finally, independent parties such as academics and non-governmental organizations can use the tools to learn more about what companies know about exposures and effects of their nanomaterials and they can use NanoRiskCat to do their own independent evaluation and subsequently engage in an informed dialogue about nanorisks with companies and regulators. It is finally important to stress that the color coding obtained in NanoRiskCat should not be seen as an absolute categorization. It rather serves as a step in an iterative process in which stakeholders in risk-related issues can reach a common – and guided - understanding of the level of potential exposures and effects of nanomaterials in specific products.

As decisions that could come out of using NanoRiskCat are stakeholder-dependent, it is important to emphasize that it has not been possible within the framework of this project to validate the NRC concept further. To promote a wider use of the tool it is considered necessary to perform additional case studies and if relevant adjust the processes and decision criteria in order to obtain a screening tool as informative and practical as possible.

1. Background and aim

Nanotechnology is an emerging technology that it is developing with rapid speed in multiple directions and in many scientific fields and industrial sectors. The term "nanotechnology" covers several methods and technologies. Some of the most well-known technologies and methods include chemical vapour deposition, atomic force microscopy and scanning probe- and tunnelling microscopy, but the number of methods, processes and techniques easily exceeds 30 (BSI 2007 a, b).

The number of nanomaterials that can be manufactured using nanotechnologies are immense including, for instance, C_{60}, carbon nanotubes, micelles, self assemble monolayers, dendrimers, and aerogels in all kinds of size and shapes. Hence the nature of nanomaterials differs even more than the techniques. In this work, we adhere to the ISO definition of a nanomaterial which defines a nanomaterial as a ***"material with any external dimension in the nanoscale or having internal structure or surface structure in the nanoscale"*** where the nanoscale again is defined as the "size range from approximately 1 nm to 100 nm" (ISO 2008).

Nanomaterials are being used in a rapidly increasing number of products available for industries and private consumers, but during the last decade more and more evidence has emerged in the scientific literature that some nanomaterials might have hazardous properties (for a comprehensive review, see Stone ***et al.*** 2009). This lead the Danish Environmental Protection Agency to identify a need for developing a new concept that can provide support to companies and regulators in regard to assessing, ranking and communicating the risks of nanomaterials in specific uses in products.

The aim of this project is therefore to develop a conceptual framework for a screening tool, NanoRiskCat, for risk evaluation, categorization and ranking of nanomaterials based on data available in the peer-reviewed scientific literature and other regulatory relevant sources of information and data. The primary focus will be on nanomaterials relevant for professional end-users, consumers as well as released to the environment. Professional end-users are defined as entities that use products containing nanomaterials professionally and are not to be understood as workers that produce the products.

There are many data gaps and unknowns in relation to specific knowledge about exposure, hazards and risks related to the use of nanomaterials. However, it is important to stress that the screening tool proposed here is intended to be used on the basis of existing experience regarding, for example, general knowledge about the exposure potential in different product types and use categories. For evaluation of potential hazards read-across from information on the bulk material will be used if appropriate in order to describe the most probable toxicological profile of the nanoform of the material. Thus hazard data on the bulk material is be used to form the basis of the minimum level of concern with regard to the nanomaterial.

The aim of this project has been to develop an easily comprehensible ap-

proach that - when fully developed and validated - can help manufacturers, down-stream end users, regulators and other stakeholders in making decisions in situations where the safety of nanomaterials are being questioned.

Before going into detail with NanoRiskCat a systematic evaluation of existing ranking and assessment concept and frameworks for chemicals and nanomaterials will be performed (Chapter 2) in order to get inspiration from these. This is followed by a description of the overall structure of NanoRiskCat (Chapter 3) as well as the evaluation criteria used to assess the exposure potential of a given nanomaterial application and to evaluate the hazard profile of a specific nanomaterial. This includes two illustrative examples of using NanoRiskCat on specific nanomaterial used in consumer products or industry (Chapters 4) and a discussion about the potential use(s) and pros and cons of NanoRiskCat (Chapter 5).

2. Existing ranking and assessment concepts for nanomaterials

Traditional risk assessment of chemicals consists of hazard identification, dose-response assessment, exposure assessment and risk characterization. Applying traditional risk assessment to nanomaterials holds a number of challenges that have yet to be overcome. Traditional risk assessment is based on the principle that the "dose [by mass] makes the poison" (Baun and Hansen 2008), but scientific evidence indicate that this might not be the case with nanomaterials (Stone ***et al.*** 2009) and that other materials properties such as size, surface area, surface chemistry, and reactivity need to be considered as well (Hansen et al 2007). Traditional risk assessment furthermore assumes that a "safe level of exposure" can be established and that human and environmental exposure can be assessed or estimated. There is disagreement about whether these assumptions are valid when it comes to nanomaterials due to lack of consensus on the appropriate hazard metric and index and report of nanomaterial exposure. According to Paik ***et al.*** (2008) and Hansen (2009) there are numerous barriers that need to be overcome before traditional risk assessment can be applied to nanomaterials and according to Hansen (2009) this might take 20-25 years. The question then becomes what to do in the meanwhile and how to report on what is known about a given nanomaterial and its uses?

A number of concepts, approaches and frameworks currently exist that intend to estimate and control to risks of nanomaterials. Examples of these includes the American "Control Banding Nanotool" developed to assess and control the risks of nanomaterials when working in the laboratory (Paik ***et al.*** 2008, Zaik ***et al.*** 2009), and the more holistic "Swiss precautionary matrix" developed by Höck ***et al.*** (2008). A number of concepts and tools also exist which were originally develop for the safe handling of chemicals such "Comprehensive Environmental Assessment" (Davis 2007) and "MultiCriteria Decision Analysis" (Linkov ***et al.*** 2007, Tervonen ***et al.*** 2009) and these might also be relevant to explore in regard to nanomaterials.

In this chapter the content of these frameworks and tools will be briefly described and finally identified pros and cons of these tool will be discussed and listed in a table for comparison. The purpose of doing this is to give an overview of existing frameworks in order to assure that the development of NanoRiskCat is developed under the consideration of the knowledge gained from the already developed frameworks. Furthermore, some of the approaches used in existing frameworks have served as a source of inspiration for the development of NanoRiskCat and this should be acknowledged.

2.1 British Standards (2007)

In 2007 British Standards published one of the first reports with actual suggestion on how to assess the hazard of handling of particulate nanomaterials in the work environment. The proposed framework is fairly simple as the purpose was to develop a set of practical guidelines.

The approach proposed follows the framework outlined in the British Control of Substances Hazardous to Health Regulations (COSHH) 2002 which comprises of eight main steps:

1. identify the hazards and assess the risks.
2. decide what precautions are needed.
3. prevent or adequately control exposure.
4. ensure that control measures are used and maintained.
5. monitor the exposure.
6. carry out appropriate health surveillance.
7. prepare plans and procedures to deal with accidents, incidents and emergencies.
8. ensure employees are properly informed, trained and supervised.

In the proposed framework the availability of information is linked to assumptions about hazards and the need for exposure controls in the sense that if little is known about the material, it will be necessary to treat it as highly hazardous and apply tighter exposure controls.

When considering the available hazard information the BSI (2007) suggests starting with categorizing nanomaterial-associated hazards into four groups:

1. Fibrous a high aspect ratio insoluble nanomaterial.
2. Any nanomaterial which is already classified in its larger particle form as carcinogenetic, mutagenic, asthmagenic or a reproductive toxicant (CMAR).
3. Insoluble or poorly soluble nanomaterials not in the fibrous or CMAR category.
4. Soluble nanomaterials not in fibrous or CMAR category.

According to the BSI (2007) it should be assumed by default that all categories of nanomaterials have a hazardous potential, which is greater than that of the larger, non-nanoscale forms of the material.

For exposure assessment, qualitative assessment of the exposure level or quantitative measurements of air concentrations with “appropriate” measuring instruments. One parameter in the exposure scenario is reserved to methods to reduce exposure whereas the rest of parameters describe the actual use phase under which is there is an exposure risk and who many might be exposed.

The calculation method to be used for estimating of the exposure risks is not described, however the BSI (2007) notes that the chosen parameters

could be insufficient given the lack of knowledge regarding nanoparticles. BSI state that an exposure assessment should ideally be based on measurements with ”appropriate” apparatus and that relevant measurements should be included in the assessment as much as possible. Given current knowledge about nanoparticles, it is likely that much of the information asked for will be considered insufficient according to BSI (2007). Hence focus of the evaluation process should be on identification of those use scenarios for which a high exposure is likely and/or highly uncertain followed by a more detailed analysis of these uses. BSI (2007) underline the necessity to err on the side of caution and to determine where significant doubt exists and develop a prioritized plan to collect additional information about exposure levels.

Based on the hazard evaluation and the exposure assessment, the BSI (2007) suggest handling of the risk following a hieratical prioritization. Priorities are decided on the basis of assessments of:

- the most serious risks to health
- the risks that are likely to occur soonest
- the risks that can be dealt with soonest

2.2. Control Banding Nanotool

In 2008 Paik ***et al.*** (2008) presented their Control Banding Nanotool which is based on the paradigm established by COSHH Essentials (HSE, 2005) as well and apply only to work environment. The backbone of Control Banding Nanotool is the concept of ‘bands’ to assist in preventing exposure to chemicals. The control band to be implemented for a given operation is based on the overall risk level (RL) determined for that operation which again is determined by a ‘severity’ score and a ‘probability’ score.

The overall severity of the nanoscale materials should be evaluated considering a number of factors such as surface chemistry, particle shape, particle diameter, solubility, carcinogenicity, and reproductive, mutagenicity, dermal toxicity of the nanomaterial itself as well as the Occupational Exposure Level, the carcinogenicity and the reproductive and dermal toxicity of the parent material. Based on available information in the literature, a severity score is given to each factors e.g. in regard to shape the highest severity score of 10 points is given to fibrous or tubular shaped. Particles with irregular shapes (other than tubular or fibrous) are given a medium severity score of 5 points and ‘compact or spherical’ nanoparticles results in 0 pts. Similarly, ‘1–10 nm’ particle diameter results in 10 points, ‘11–40 nm’ results in 5 points,41–100 nm’ results in 0 points and a rating of ‘unknown’ results in 7.5 points. 0 points were assigned as an indication of low ‘relative’ severity and does not indicate that no effect has been observed. If the information for a given factor is ‘unknown’, 75% of the point value of ‘high’ would be given for that factor.

The overall severity score is determined based on the sum of all the points from the severity factors and the maximum score is 100. An overall severity score of 0–25 was considered low severity, an overall severity score of 26–50 was considered medium severity, an overall severity score of 51–75

was considered high severity and an overall severity score of 76–100 was considered very high severity.

A combination of severity and probability leads to an overall risk level (RL) ranging from 1 to 4 for which specific control strategies are prescribed i.e. RL1= General ventilation, RL2= fume hoods or local exhaust ventilation, RL3= containment and RL4= seek professional advice.

For a hypothetical nanotechnology operation for which nothing was known (other than it involves nanoparticles), the required control would be 'containment' (RL3). In this scenario, if just one rating for any of the factors was later determined to be high, with all other ratings remaining as unknown, the tool would assign this activity as 'seek specialist advice' (RL4) and require the maximum control.

2.3. The Swiss Precautionary Matrix

The Swiss Precautionary Matrix developed of Höck ***et al.*** in 2008 and revised in 2010 (Höck ***et al.*** 2010) was published almost at the same time as the Control Banding Nanotool, but the Swiss Precautionary Matrix also addresses risks to consumers and environment. The stated purpose of the Swiss Precautionary Matrix is to develop a system that enables users (i.e. businesses) to estimate the "nanospecific precautionary need" of synthetic nanomaterials and their applications for employees, consumers and the environment, based on a number of selected parameters. The need for precaution is estimated for a normal use and worst-case (WC) scenario and is seen as a function of the:

1. Potential effect (W)
2. Potential human exposure / potential input into the environment (E)
3. Nano-relevance (N)
4. Specific framework conditions: Information about the life cycle (S)

It is assumed that nanospecific risks arise only if there is a possibility of two-dimensional (nanorods) or three-dimensional (nanoparticles) nanoscale particles or their agglomerates being released. Nanoscale is recommended to be extended to 500 nm (Höck ***et al.*** 2010).

The Precautionary Matrix is made up of modules of various input parameters that have to be scored by the user from 1 to 9 (low = 1, medium 5, high = 9 or hours =1, days-week=5, months=9) for the purpose of calculating the precautionary need. A template for the precautionary matrix is available as a hard copy and as a computerized version available at:
http://www.bag.admin.ch/themen/chemikalien/00228/00510/index.html?lang=de

When filling out the matrix, users are advised to carry out their own investigations on human exposure, inputs into the environment and the effects of nanomaterials as well as draw on data from the literature and experts, if applicable. If the requested information is not available, the value that

would ultimately give the highest precautionary need must be used (Höck ***et al.*** 2010).

Assigning scores to the various input parameters is of key importance and the guideline for how to apply the Swiss Precautionary Matrix offer various guidance on how to derive scores. For instance, the potential effect of nanoparticle and nanorods on health and the environment is estimated by:

1. Redox activity and/or catalytic activity of the nanoparticles and rods present in the nanomaterial.
2. Stability of the nanoparticles and rods present in the nanomaterial under the relevant conditions in the body or the environment.

As there are currently no internationally approved methods for determining the nanospecific redox activity or catalytic activity of nanoparticles and rods, an approximate evaluation can be achieved with the following the listing of comparative nanoparticles and rods set forward by Höck ***et al.*** (2010).

Stability is evaluated in regard to half-life of the nanoparticles and rods present in the nanomaterial in the body or under environmental conditions taking into account the resistance of the nanoparticles and rods used to dissolution, chemical or physical change, sintering or particle degradation.

The exposure part of the Swiss Precautionary Matrix is rather simple and based on estimation of the actual (worst-case) airborne exposure or exposure over the course of 24 hours or a workday, if talking about workers.

The exposure level is estimated from the type of exposure, the measured or estimated exposure and frequency. In regard to type of exposure, one can chose between nanomaterials in the form of airborne dust, suspended in liquids, and more or less stable matrixes. The first two type of exposure both lead to a full inhalation risk, whereas the later two gives a relative inhalation risk of free nanomaterials ranging from 0.0001-10 %. This, however this is highly uncertain and depends heavily on the material and the activity. The score given in regard to the type of exposure (e.g. 1 for airborne dust of nanomaterials) is multiplied with the score given to the level of daily exposure (<25μg = 1 point), <250 μg = 5 point; >250 μg = 9 point) and frequency of exposure (daily = 9 point, weekly= 5 point or monthly = 1 point). The limits for exposure are increase by a factor 10 in regard to estimation of exposure during an accident.

Once all the input parameters have been scored, the precautionary need can be calculated by multiplying the potential effect (W) with the potential human exposure/input into the environment (E). Then Specific framework conditions: Information about the life cycle (S) is added and the sum is multiplied by the Nano-relevance (N):

$$V = N * (W * E + S)$$

Based on the total score of the precautionary need (V) a general classification can then be made of various use of nanomaterials into a Class A and a Class B (see table 1).

Table 1: Classification of nanomaterials based on overall score in the Swiss Precautionary Matrix (Höck *et al.* 2010)

Score	Classification	Importance
0-20	A	The nanospecific need for action can be rated as low even without further clarification
>20	B	Nanospecific action is need. Existing measures should be reviewed, further clarification undertaken and, if necessary measures to reduce the risk associated with manufacturing, use and disposal should be implemented

Höck ***et al.*** (2010) does not offer a model for risk handling, but a closer look into whether there is a real nanospecific risk is recommended if the score exceeds 20 point. Hence, a weekly handling of nanomaterials with a intermediary daily airborne exposure of 25 - 250 µg would require a closer evaluation of the nanospecific risk, but not a monthly handling which gives more than 250 µg.

As a general rule, a precautionary matrix applies to just one specific type of nanoparticles and rods in a precisely defined environment. If the physical environment (e.g. solvent, matrix/substrate, state of aggregation, etc.) or the conditions of use change, a new precautionary matrix has to be completed for this situation. A new matrix also has to be completed if the original nanoparticles and rods are changed into defined new nanoparticles and rods during use, for instance through rapid dissolution of a coating.

The precautionary matrix can however be used to estimate the precautionary need for the health of employees and consumers and for the environment throughout a nanomaterial's entire life cycle. A separate precautionary matrix must be created for each process under review.

2.4 Genaidy *et al.* (2009)

Genaidy ***et al.*** (2009) represent an example of a qualitative risk assessment method which has successfully been applied in a company producing Carbon Nanofiber (CNF). In contrast to the other methods presented here, Genaidy ***et al.*** (2009) also considers the application of other chemical and other phases ranging from production to storage of bags.

The approach suggested by Genaidy ***et al.*** (2009) consists of a phase 1 focused on generation of improvement actions and a phase 2 focused on transformation of improvement actions into health education awareness and combined health protection/promotion interventions.

The first phase consists of three steps. In the first step the 'probability' of exposure and the 'severity' of consequences of workers' exposure to physical and non-physical related hazards is assessed using a hazard analysis instrument termed a "HAI". Each hazard is evaluated in terms of:

1. probability of exposure using one of five descriptors, i.e. "Frequent", "Probable", "Occasional", "Remote", and "Improbable"; and
2. severity of consequence in terms of four levels, i.e. "Catastrophic", "Critical", "Marginal", and "Negligible".

The second step of phase 1 involves the transformation of hazard measurement into a risk code as follows:

1. The probability of exposure and severity of consequences for a given hazard or work environment characteristic are entered into a risk map derived by Genaidy ***et al.*** (2009) on the basis of knowledge extracted from a number of consensus meeting with risk assessment experts;
2. A risk code is determined depending on the probability–severity values. There are five risk levels (Abdallah ***et al.***, 2004):
3. "Very high" or "red" — substantial changes should be planned immediately followed by incremental changes;
4. "High" or "orange" — substantial changes should be planned in the short term, followed by incremental changes;
5. "Moderate" or "yellow" — one should start with incremental changes then explore substantial changes if needed;
6. "Low" or "blue" — one should explore incremental changes;
7. "Very low" or green" — sustain the current situation.

During the third step of phase 1 the Risk scores are classified into two-tier classification:

1. Risk score b3 (i.e., "very high", "high", and "moderate"), and
2. Risk score N3 ("low and very low")

The two-tier classification along with the priority scores of improvement actions from step 1 is used to identify:

1. short-term improvement actions — high-priority (step 3a) and medium-priority (step 3b); and,
2. long-term improvement actions step 3c.

The former address the "red" and "orange" priority levels of hazards and the methodology applied focuses on reducing the red and orange scores into blue in the short term with no lesser value than "3" or yellow. Step 3b address the yellow scores into blue in the short term whereas step 3c calls for continuous improvement to change blue characteristics into "green", if possible (Genaidy ***et al.*** 2009).

In contrast to the other methods and approaches presented here, the approach suggested by Genaidy ***et al.*** (2009) offers a prescribed approach for handling of identified risks during phase 2. Improvement actions are however not automatically prescribed as in the case on the approaches using

Control Banding concepts. Instead, improvement actions is expanded on by adding the type of intervention (e.g. health protection/promotion/education awareness) and the criteria required for their implementation and the proposed approach makes use of the strategies researched by Haddon (1973, 1980) for the reduction of risks arising from hazards of all kinds. The strategies include: (1) elimination of hazard creation; (2) reduction of the amount of hazard brought into being; (3) prevention of hazard release; (4) modification of distribution rate and spatial of hazard release from its source; (5) hazard separation via time or space; (6) hazard separation by interposition of a material barrier; (7) modification of relevant basic qualities of hazard; (8) rendering the target to be protected more resistant to damage from that hazard; (9) counter damage already done by environmental hazard; and, (10) to stabilize, repair and rehabilitate the damaged object.

For each of the intervention strategies four criteria were applied: applicability, benefit, cost and feasibility. If one of Haddon's strategies is considered applicable the other criteria are considered. For the evaluation of benefits and cost, Genaidy ***et al.*** (2007) suggest that preference is given to any high benefit/low cost strategy (Option I) followed by any high benefit/high cost (Option II) and low benefit/low cost (Option III) strategy and finally low any benefit/ high cost (Option IV) strategy. Feasibility is used as a final criterion and should be accessed in the short-term (yes) as well as in the long-term (no).

2.5 MultiCriteria Decision Analysis and risk-based classification system for nanomaterials

A number of multiple criteria decision analysis (MCDA) methods exist and a common purpose of these methods is to evaluate and choose among different decision alternatives based on multiple criteria using systematic, structured and transparent analysis in contrast to ''ad hoc'' decisions (Linkov ***et al.*** 2006, Hansen 2010). MCDA methods vary in regard to various optimization algorithms deployed, in the types of value information needed and in the extent to which they are dependent on computer software. Some MCDAs techniques rank options against each other whereas others identify a single optimal alternative and again others differentiate between acceptable and unacceptable alternatives (Linkov ***et al.*** 2007). Linkov ***et al.*** (2007) have illustrated the theoretical applicability of MCDA to evaluate three hypothetical nanomaterials whereas Tervonen ***et al.*** (2009) have used an outranking model termed Stochastic multicriteria acceptability analysis (SMAA-TRI) to group nanomaterials (e.g., C_{60}, MWCNT, CdSe) in various risk classes (extreme, high, medium, low, and very low risk) for screening level risk assessments. More specifically, Tervonen ***et al.*** (2009) set forward a number of criteria, both in terms of nanoparticle properties as well bioavailability, bioaccumulation and toxic potential. Quantitative criterion were either measured or based on expert judgments whereas qualitative criteria were established in terms of ordinal classes: 1 was the most favourable (least risk) value class, while 5 the least favourable (highest risk). Weight bonds were assigned to the various criteria by the authors e.g. toxic

potential 0.3–0.5, bioavailability and bioaccumulation potentials 0.02-0.08 and the rest of the criteria were assigned weight bounds of 0.05–0.15. A cutting level within the range of 0.65–0.85 was then used to define the minimum sum of weights for the criteria that must be in concordance with the outranking relation to hold.

2.6 Environmental Defense & DuPont Nanorisk framework

An example of a framework that has already been used by industry is the Nano Risk Framework which was jointly released in early 2007 by Environmental Defense and the DuPont Corporation (Environmental Defense and DuPont 2007). This framework describes a process for "ensuring the responsible development of nanoscale materials." (Environmental Defense and DuPont 2007). The framework can be used freely by companies and other organizations. The intent of the framework "is to define a systematic process for identifying, managing, and reducing the potential environmental, health, and safety risks of engineered nanomaterials across all stages of a product's 'lifecycle'." It is meant to offer a voluntary approach to facilitate the responsible development of nanomaterials by companies, as well as private and public research institutions. The framework is designed to be used iteratively at different stages of development advancement including basic R&D, prototyping, pilot testing, test marketing, and finally full-scale commercial launch as well as when new information becomes available.

The framework consists of six distinct steps:

1. Develop a general description of the nanomaterial and its intended uses, based on information already available, and identify analogous materials and applications that may help fill data gaps in this and other steps.
2. Develop profiles of the nanomaterial's properties, inherent hazards, and associated exposures, considering all the elements of the nanomaterial's full lifecycle and also considering that a material's properties, hazards, and exposures may change during.
3. Evaluate all of the information generated in the profiles and identify and characterize the nature, magnitude, and probability of risks of the nanomaterial and its application. Gaps in the lifecycle profiles should be prioritized and a decision should be made on how to address them.
4. Evaluate the available risk management options and recommend a course of action, including engineering controls, protective equipment, risk communication, and product or process modifications.
5. Decide alongside key stakeholders, experts, and decision-makers whether or not, or in what capacity, to continue development and production and document these decisions as well as their rationale, and share appropriate information with relevant stakeholders.
6. Update and re-execute the risk evaluation regularly or as necessary to ensure that risk management systems are working as expected and adapt in the face of new information or conditions.

The authors clarify that, ***"[t]hrough these six steps, the framework seeks to guide a process for risk evaluation and management that is practical, comprehensive, transparent, and flexible."*** (Environmental Defense and DuPont 2007). The ED and DuPont framework is further intended to guide users through information generation and help them update assumptions, decisions, and practices as new information becomes available. At various stages in the product-development process, the document provides a worksheet to help participants: 1) organize, document, and communicate the information they have about their material; 2) acknowledge that information is incomplete; 3) explain how information gaps were addressed; and 4) explain the rationale behind the user's risk management decisions and actions.

The amount of information required in the framework is directly related to the potential extent and degree of exposure of the specified application. ED and DuPont recommend that a broad range of stakeholders have access to the worksheet or summaries of it as products move into commercialization in order to facilitate ease of understanding. DuPont has made it clear that it fully supports this framework. In fact, DuPont has made the framework standard for its own operations involving nanomaterials. In at least one instance, applying the framework indicated that a product's development should be halted (Fisher 2007).

2.7 Pros and cons of existing tools and frameworks

In Table 2 we have summarized the key characteristics of the various tools, approaches and frameworks in regard to focus, methods, hazard and exposure evaluation input parameters, risk evaluation and risk handling, etc. as well as their pros and cons in regard to the scope of this project. When comparing the pros and cons of existing tools and frameworks it is important to note that such a comparative analysis can never do full justice to the all tools and frameworks. The methods, approaches and frameworks presented here are all helpful in to the primary evaluation of the potential hazards, exposures and risks related to production and application of nanomaterials although they might not all be equably helpful in relation to meeting the purpose of this project. Many of the tools such as e.g. Genaidy ***et al.*** (2009) and the Nanorisk framework (ED & DuPont 2007) are developed in order to help developers and producers of nanomaterials complete crude risk estimations. Whereby the hope is that this will make developers and producers focus on minimizing exposure or facilitate the implementation of various more or less stringent control measures to protect workers in the primary production and handling of nanomaterials. Only some of the methods and frameworks (e.g. the Swiss Precautionary Matrix and the MCM risk-based classification system) involve professional end-users, consumers and the environment which are the subject of this project.

Although varying greatly in focus and scope, most of the approaches and frameworks provide guidance on how to make a crude assessment of the hazards and exposure associated with a nanomaterials and its use(s). In re-

gard to the hazard of nanomaterials, all but the framework proposed by Genaidy ***et al.*** (2009) set up a series of criteria or hazard endpoints that have to be considered. It is however not always clear why a given criteria was included or excluded from the analysis. Furthermore, some of the criteria are based on mass, which many of the authors of proposed frameworks themselves state is not sufficient to deal with nanomaterials. Among other the Swiss Precautionary Matrix, the MCM risk-based classification system and CB Nanotool assign numbers or ranges to the extent of various reported effects, which makes the frameworks easy and transparent to use in the sense that these numbers are assigned to various effects by default and the scoring process can be validated by others. How the numbers or ranges have been assigned to the various effects is less transparent.

In regard to exposure of nanomaterials, most approaches and frameworks use an estimate of the likelihood of exposure or a more-or-less precise relative scale. These are useful to identify activities with potential risks of exposure, as it has been shown with the completely qualitative model proposed by Genaidy ***et al.*** (2009). A weakness of these tools is however that they do not provide a strong tool for estimating an actual exposure level. It could be a great help to identify whether for instance a high likelihood for exposure also gives cause to a "high exposure". Control Banding Nanotool provides the possibility of assessing the exposure level based on the amount of material handled and the frequency of the activity. The English system developed by BSI and the Swiss Precautionary Matrix use either a simple assessment or actual exposure measurements. Actual exposure measurements require the use of a series of fairly complex measurement methods to estimate the fraction of the nanomaterial that become airborne at the workplace. The development of quantitative model would make it possible to complete solid exposure assessments before nanomaterials are used in a large scale. New methods are under development and hopefully they will help solve some these problems, but there is a long way in areas like consumer exposure and environmental exposure modelling before we reach the level of the models that are now available for assessing human to fine and ultrafine particles.

Combining the hazard and the exposure assessment, all of the tools and frameworks derive an overall score, which is then again linked to a categorization e.g. A, B, C, or high, medium, low. The categorization makes the results of using the tool easy to summarize and communicate on the one hand, but also risks masking the process by which the categorization was derived. Thereby the scientific analysis of the available evidence of human and environmental hazards goes in the background as so does the line of argumentation used to derive the overall score and subsequent categorization. A number of frameworks translate the overall score into a set of recommendations for general prescribed management measures. Such an approach is e.g. explored in the Swiss Precautionary Matrix and the CB Nanotool. In order for these recommendations to be generic they have to be very broadly defined, which risks making them too general and non-specific to give input to real decision support.

Common for most of the concepts available today is that their input data requirements are fairly high and some of the scientific information needed in order to apply them is inconclusive at the moment or non-existing. Lack of information and data is the reality even for the nanomaterials that are applied in high quantities today.

Some of the concepts are furthermore based purely on theoretical considerations and time-consuming to apply in reality. This underlines the importance of developing a new, step-wise and more transparent decision-making tool to evaluate the exposure and hazards of nanomaterials to human health and the environment. It is however important to learn from these concepts and learn from the experiences made with these, in order to make sure that a new decision-making tool is up-to-date, transparent, and applicable.

Table 2: Summary of the main characteristic of the different frameworks

Name	BSI Nanomaterials Handling Guide	CB Nanotool	Swiss Precautionary Matrix
Reference	BSI (2007)	Paik *et al.* (2008)	Höck *et al.* (2008)
Focus/ Applicability	Work environment	Work environment	Workers, consumers, environment
Scope	Nanoparticles	Nanoparticles	Nanoparticles and nanorods
Method	Qualitative/quantitative	Qualitative/quantitative	Qualitative/quantitative
Strategy	Hazard evaluation + Exposure assessment + Handle risk	Hazard evaluation Exposure assessment + recommended risk handling	Hazard evaluation + Exposure assessment+ Assessment risk handling need
Exposure assessment input parameters	1)Describe work procedure 2) Who is exposure? 3) What is the exposure route (inhalation, oral, dermal)? 4) When does exposure occur? 5) Frequency of exposure 6) Level and extent of exposure[8] 7) Source of exposure potential 8) Protection possibility	1) Determine number of employees in completing the activity 2) Frequency of the activity 3) Time extend of activity 4) Amount of nanomaterial used in each cycle of the activity 5) Dustiness index or evaluation of mistiness	1) Type of exposure (air, liquid or in a matrix)? 2) Amount of nanomaterial a worker normally exposed to during a day? 3) How much nanomaterial can a worker be exposed to in a worst case?
Scale assessment of exposure level	Assess (estimate) or do measurements	Linear 4-step scale calculated based on points given for the five exposure parameter/ measurements	For airborne exposure the risk is scaled by the 2 remaining parameters under normal circumstances and accidents
Hazard evaluation input parameter	CMAR Fibrous Insolble Soluble	Surface chemistry Particle shape Particle diameter Solubility CMAR(nano- and bulk materials) Dermal toxicity (nano- and bulk materials) Occupational Exposure Level	Redox activity and/or catalytic activity Stability in physiological and environmental conditions
Scale evaluation of hazard evaluation	None	1) Assign severity factors btw 0-10 p., 2) derive overall score btw 0-100 p., 3) assign probability estimate (0-100)	Input parameters are scored btw 1-9
Risk evaluation	Categories into the 1) most serious risks to health; 2) risks that are likely to occur soonest; and 3) risks that can be dealt with soonest	Combine severity score and probability score into four possible risk levels (RL)	Total score of the precautionary need V = N * (W * E + S) and classified as "A" (V= 0-20) and "B" (V> 20)
Risk handling	"Hierarchical risk handling" based on COSHH principles	Control bands and exposure control	Unspecified
Special circumstances	Nanomaterial specific maximum exposure standards	Unknown parameters is assigned 75 % of the maximum score	Nanoscale is extended to 500 nm; Unknown parameters is assigned 100% of the high risk score; Actual/estimated daily or worst case inhalation exposure – and not material quantity
Pros	Pro-active in the sense that risk handling can be implemented immediately	High usability, Pedagogical color code, clear results that limit "paralysis by analysis"	Step-by-step guide is clear and easy to apply; considers workers, consumers, environment as well as taking a life-cycle perspective
Cons	Relies on having good information about the hazardous nature of materials, the effectiveness of control approaches and convenient and accessible ways to monitor exposure. This information might not always be available	Unclear how severity scores and probability were assigned e.g. to particle shape and dustiness and not clear why unknown parameters is assigned 75 % of the maximum score	Questionable use of default values for the redox activity or catalytic activity; Unclear why unknown parameters is assigned 100% of the high risk score; Questionable quantitative derivation of whether there is a precautionary need for action; Overall classification scores seems arbitrary

Table 2: Summary of the main characteristic of the different frameworks continued

Name		**Nanorisk framework**	**MCM risk-based classification**
Reference	Genaidy *et al.* (2009)	ED & Dupont (2007)	Tervonen *et al.* (2009)
Focus/ Applicability	Work environment	Workers, consumers, environment	Human and environment
Scope	Nanomanufcaturing operation	Nanoapplications and products	Nanoparticles
Method	Quantitative	Qualitative/quantitative	Qualitative/quantitative
Strategy	Hazard evaluation + Exposure assessment + Handle risk	Describe, evaluate and decide, update and re-execute life-cycle hazard-, exposure- and risk profiles	Select and define criteria, identify options, rank options in regard to criteria, select optimal option(s)
Exposure assessment input parameters	Not specified	Among other: 1) Number and locations of manufacturing sites 2) Current and expected production 3) Industrial function 4) Maximum concentration used 5) required controls, etc.	Not applicable
Scale assessment of exposure level	Logarimic 5-step scale (US DOD *Mishap probability levels")*: Frequent, Probable, Occasional, Remote, Improbable	Not specified	Not applicable
Hazard evaluation input parameter	Not specified	Short-term tox, skin sensitization/irritation, skin penetration, genetic toxicity tests, biological fate and behavior, chronic inhalation/ingestion /dermal tox studies, Developmental and reproductive toxicity studies, Neurotox studies, genotox studies and endocrine-disruption studies	Agglomeration and aggregation, reactivity, critical functional groups, particle size, and contaminant dissociation, size, bioavailable and bioaccumulation potential and toxic potential
Scale evaluation of hazard evaluation	Catastrophic (Deaths); Critical (Severe injuries or illness); Marginal (Minor injury or illness); Negligible (No illness or injury)	Not specified	Particle size evaluated as the mean size of the material in units of nanometers and expert estimates. All other criteria were scored from 1 to 5 via expert judgment. 1 was the most favorable (least risk), while 5 the least favorable (highest risk).
Risk evaluation	A risk code is determined depending on the probability–severity values. There are five risk levels e.g. "Very high" or "red"; "High" or "orange", etc.	Evaluate nature, magnitude and probability of risk types	Classification into extreme, high, medium, low, and very low risk categories
Risk handling	Haddon's system	Focused on minimizing exposure	Unspecified
Special circumstances	For each of the intervention strategies four criteria were applied: applicability, benefit, cost and feasibility	Sharing of product info, hazard, exposure and risk profiles with stakeholders is recommended	Uses an outranking model termed Stochastic multicriteria acceptability analysis (SMAA-TRI)
Pros	Scenarios are illustrated as activity appellations without any further description of the circumstances	Clear guide on how to organize, document, and communicate information	High level of transparency in selection of criteria and enables the users to define their own criteria
Cons	Unclear hazard input parameters and assignment of risk codes	High data requirements often not available, unclear how to evaluate nature, magnitude and probability of risk types, independent validation by stakeholders hard	Low level of transparency in the qualitative assignment of scores between 1 and 5 to various nanomaterials. Unclear how specific weight bonds were assigned

3. NanoRiskCat

It is the aim that NanoRiskCat will enable companies, regulators and independent parties to identify, categorize, rank and communicate any eventual risk associated with the specific application(s) of a given nanomaterial by sequentially mapping and reporting in the:

1. Exposure potential for professional end-users
2. Exposure potential for consumers
3. Exposure potential for the environment
4. A preliminary hazard evaluation for humans
5. A preliminary hazard evaluation for the environment

A generic template for mapping and reporting these five aspects for a specific application of a given nanomaterial has been developed and can be found in Appendix 1 of this report. In its simplest form the final outcome of using NanoRiskCat for a nanomaterial in a given application will be communicated in the form of a short title describing the use of the nanomaterial (e.g. MeO in ship paint) and five color-coded dots (e.g. ●●●|●●). The first three colored dots refer to potential exposure of professional end-users, consumers and the environment, respectively, whereas the last two colored dots refer to the hazard potential for humans and the environment, respectively. The dots can have four different colors assigned to them by the user of NRC: Red (●), yellow (●), green (●) and grey (●). The red, yellow and green colored dots respectively indicate high, medium and low indication of exposure or effect whereas the grey indicates that the data available is too limited to assess the possibility for exposure or effect.

The color coding principle in NanoRiskCat is shown in the table 3 below:

Table 3: Color coding principle in NanoRiskCat. Assignment of colors is based on the methodology provided in Chapter 3.2 (exposure potential for professional users, consumers, and the environment), 3.3 (human health effects), and 3.4 (environmental effects).

Exposure indication			**Effect indication**	
Professionals	**Consumers**	**Environment**	**Human health**	**Environment**
<color> ●	<color> ●	<color> ●	<color> ●	<color> ●
			<sentence from list below>[a)]	<sentence from list below>[b)]

[a)] Refer to a list of default sentences that can help NRC users to communicate on which kind of evidence the color coding for human health hazard is based (see Appendix 2, Table A2.1)

[b)] Refer to a list of default sentences that can help NRC users to communicate on which kind of evidence the color coding for environmental hazards is based (see Appendix 2, Table A2.2).

Box 1. Example of the use of NanoRiskCat for categorization of the exposure and hazard potentials of two different nanomaterials used in ship paints (hypothetical cases)

For the use of two different nanomaterials (hypothetical materials denoted MeO and FO) in ship paints the following two NanoRiskCat profiles may be obtained

MeO in ship paint

Exposure			Effects	
Professionals	**Consumers**	**Environment**	**Human health**	**Environment**
●	●	●	●	●
			4[a)]	6[b)]

a) "based on bulk CLP classification 1 or 2 for carcinogenicity"
b) "based on bulk CLP classification of Chronic 3 or Chronic 4 and $T_{1/2}$ > 40 d"

FO in ship paint

Exposure			Effects	
Professionals	**Consumers**	**Environment**	**Human health**	**Environment**
●	●	●	●	●
				12[b)]

b) "based on bulk CLP classification of Chronic 3 or Chronic 4 and an evaluation of dispersive or long range transport, ecosystem effects and novelty"

Red, yellow and green colored dots indicate high, medium and low indication of exposure or effect whereas the grey indicates that the data available is too limited to assess the possibility for exposure or effects. Hence in the first case there is a medium indication of exposure towards professional end-users and consumers, whereas the indication of environmental exposure is expected to be high. The indications of effects from the nanomaterial as such in relation to both human and the environment are expected to be high.

In the second case the exposure profile is the same as in the first case, but the indication of adverse effects on humans is low and there is insufficient knowledge and data to evaluate the possibility of environmental effects.

The two examples consider the same use and form of application and the exposure profiles are therefore the same for the two materials (i.e. ●●●). A comparative analysis of the hazard profile of the two materials would suggest that it is preferable or "more safe" to use FO in ship paint. This is due to the human hazard profile for MeO is "red" vs. "green" for FO whereas the environmental hazard profile for MeO is "red" vs. "grey" for FO. However, to make such final conclusion it is necessary to take account of the respective concentrations of the nanomaterial in the products, the hazardous properties and the concentration of the other constituents in the products and whether there are any differences in the handling and the exposure potential between the products. Thus the screening tool gives an indication that has to be further verified before a final decision can be made.

The purpose of the development of NanoRiskCat is to create a generic framework, which can be applied for specific application(s) of specific nanomaterial(s). Although NanoRiskCat is a qualitative tool, quantitative values should and can be applied in the criteria setting for the assignment of color code.

It is important to underline that NanoRiskCat is not a product label and NanoRiskCat is only to be used for evaluating the nanomaterial as an ingredient under the physical conditions it occurs in the product (e.g. in a liquid suspension or embedded in a solid matrix). For example, the use of nanoscale titanium dioxide in sun lotion or in varnish products, cerium oxide used as a diesel additive, or nanosilver in textiles can be evaluated using NanoRiskCat in a generic way, thus NanoRiskCat is applicable for all types of commercial products. However NanoRiskCat does not take account for the exposure and hazard for the other constituents in the product, nor the additives or impurities. NanoRiskCat is directed towards the generic use descriptors and scenarios, which for instance are apparent in the product categories used in REACH. Thus, NanoRiskCat furthermore does not consider whether the content of the nanomaterial is low or high in the product nor does it evaluate exposure and hazard from the other constituents and impurities in the product, as such an evaluation would require exposure scenario specific risk assessments for the substances included in the products according to the conventional methodology described in REACH.

It is the hope that NanoRiskCat will contribute to the safe handling of nanomaterials in specific applications and it is important to underline that filling out NanoRiskCat cannot be used to pass judgment about the safety of all applications of a given nanomaterial.

While information on inherent physico-chemical and biological properties is needed to complete full hazard identification, it has to be recognized that there is a general lack of information on nanomaterials and thus many unknowns exist. A screening tool that takes outset in the requirements for performing traditional risk assessment (i.e. hazard identification derived from inherent physico-chemical properties followed by exposure and effects assessments) would therefore in most cases fall short and end up in a conclusion that additional input data are required. This counteracts the desire for providing timely guidance to companies, regulators and interested parties based on available data.

Therefore a fundamental principle of NanoRiskCat is to exploit existing knowledge and data to the full extent possible in an approach that assesses which applications of nanomaterials that, on a relative scale, are more problematic than others.

This is done by adapting the traditional paradigm in risk assessment of chemical substances, i.e. risk expressed as the relationship between hazard and exposure, in such a way that a qualitative exposure evaluation (for defined subgroups i.e. professional end-users, consumers and the environment) is performed before traditional hazard identification is carried out. Focus is on establishing the exposure potential based on the assumption that we know a lot more about the application of nanomaterials in various products than we do about their fate in the environment and their toxicological and ecotoxicological hazard potentials.

This principle has also previously been identified by the British Standardization Institute (BSI, 2007), who stated that:

"***The likelihood (or risk) of disease occurring depends on the dose of the particles in the organ where disease can occur, and the toxicity of nanoparticles. (…) If there is no exposure (i.e. no nanoparticles in the air), no dose will accumulate and, despite the potential toxicity of the particles, there will be no risk to health. It therefore follows that an appropriate response to the risks from nanomaterials is to understand the potential exposures which could arise from the manufacture and use of nanomaterials and to put in place measures to mitigate, manage or reduce exposure. In this way the risks can be controlled.***" (BSI 2007)

For each application of a specific nanomaterial, the use of NanoRiskCat has to describe the specific nanomaterial produced and/or used, specify use scenario(s), and complete an evaluation of the exposure potential professional end-users, consumers and the environment as well as, if possible, establish a toxicological and ecotoxicological hazard profile of the specific nanomaterial. The short title describing the use of the nanomaterial (chapter 3.1) combined with the exposure (chapter 3.2) and the hazard profile (chapter 3.3) will give a color code that summarizes the hazard profile of the specific application of the nanomaterial. Each of these elements will be introduced in the following.

3.1 Short titles for use scenario(s) and nanomaterial identification

In order to provide an evaluation of the hazard profile and provide an evaluation of the exposure potential for professional end-users, consumers and the environment background information on the nanomaterial(s) and its specific use(s) is needed.

First of all, the NanoRiskCat subject should be clearly specified in the form of a short title, defining the specific kind(s) of nanomaterial(s) under analysis and their use(s). This should be communicated in the form a short title describing the use of the nanomaterial. The short title could be general e.g. "TiO_2 nanoparticles used in sunscreens" or very specific e.g. (hypothetical example) "40 nm rutile TiO_2 nanoparticles used in Engima SunProtection Factor 50". The important thing is that it is clearly stated which nanomaterial and which use/application is subject for the evaluation. Schemes for reporting such information already exist, for instance NANOSAFER developed by National Research Centre for the Working Environment and Danish Technological Institute (Industriens Branchearbejdsmiljøråd 2011) or the Nano Risk framework developed by Environmental Defense and DuPont (2007) (see "Section 1: Describe Material and Its Applications").

Second, some basic information and consideration is needed regarding the production of the nanomaterial and the products containing the specific nanomaterial as well as known use(s) and expected route of disposal routes of the products containing the nanomaterial. This includes information about the nanomaterial in its pristine form as well as in the form it is used by consumers and/or professional end-user. Information must be provided on at least: the known professional and non-professional uses of the product, release information, information about who handles a product at what stage of its use(s) and applied and/or required personal protection equipment (PPE). A

schematic overview of key elements in the life cycle of the nanomaterial in the specific use scenario may also be provided. Guidance on how to complete such an analysis can be found in Section 2: Profile Lifecycles of the Nanorisk framework developed by Environmental Defense and DuPont (2007), see Table 3 below.

Table 3: Table to be filled in for identification of material life-cycle stage in the given application. Adapted from "Section 2: Profile Lifecycles" of the Nanorisk framework developed by Environmental Defense and DuPont (2007).

Material life-cycle stage	Description
Material Sourcing (e.g. producer, supplier)	<to be filled in by the user>
Manufacturing (e.g. processing, product fabrication, filling/packaging)	<to be filled in by the user>
Distribution	<to be filled in by the user>
Use/maintenance/reuse	<to be filled in by the user>
Disposal/Recycling	<to be filled in by the user>

3.2 Criteria for evaluating the exposure profile

Based on the information provided in the previous section, the exposure potential for professional end-users, consumers and the environment should be assessed and assigned a color code accompanied by a clear explanation of why the chosen color reflects what is currently known about exposure.

Specific knowledge about the exposure situation is of course first choice for the exposure evaluation. Where such information is not available the generic approach sketched here should be used to evaluate the exposure potential for professional end-users, consumers and the environment. The exposure evaluation in NanoRiskCat takes outset in the use descriptor system established by ECHA in the current REACH Guidance on information requirements and chemical safety assessment Appendix R.12 (ECHA 2010). In brief, the use descriptors are those categories of use that the producer or importer of a substance has registered the compound in, i.e. what is the substance going to be used for? There are five separate lists of descriptors with a number of sub-categories, but not all the various categories are equally relevant for professional end-users, consumers and the environment when it comes to nanomaterials. Table 4 lists the use descriptors recommended in NanoRiskCat.

Table 4: Overview of relevant use descriptor for an evaluation of potential exposure of professional end-users, consumers and the environment in NanoRiskCat. Use descriptors are selected among those listed in ECHA (2010).

Use Descriptor Categories in REACH	Prof. end-users	Consum-ers	Environ-ment
Process (PROC)	X		
Product (PC)	X	X	
Technical functions (FC)	X		
Article, no intended release (AC)	(X)	(X)	X
Articles, intended release (AC)	(X)	X	X
Environmental Release (ERC)			X

For each use category, a color code (●, ●, ● or ●) has been assigned based on 1) the location of the nanomaterial (bulk, on the surface, liquid or airborne) and 2) a judgment of the potential for nanomaterial exposure based on the description and explanation of each process, product category, technical function, article and environmental release category provided in the REACH Guidance. Tables of use categories and the default color codes assigned to each use category are shown in Appendix 3.

As mentioned above, this categorization is based partly on the description and explanation associated with each process (PROC), product category (PC) and technical functions (FC), etc. and partly on an assessment of the exposure potential of the use of a given nanomaterial used in a specific process, product and/or technical function following the framework developed by Hansen ***et al.*** (2007, 2008). The framework developed by Hansen ***et al.*** (2007, 2008) is based on categorizing nanomaterials according to location of the nanomaterial (see Figure 1) and grouping applications of nanomaterials into four different exposure categories:

1. expected to cause exposure
2. may cause exposure
3. no expected exposure
4. unclassifiable due to lack of information

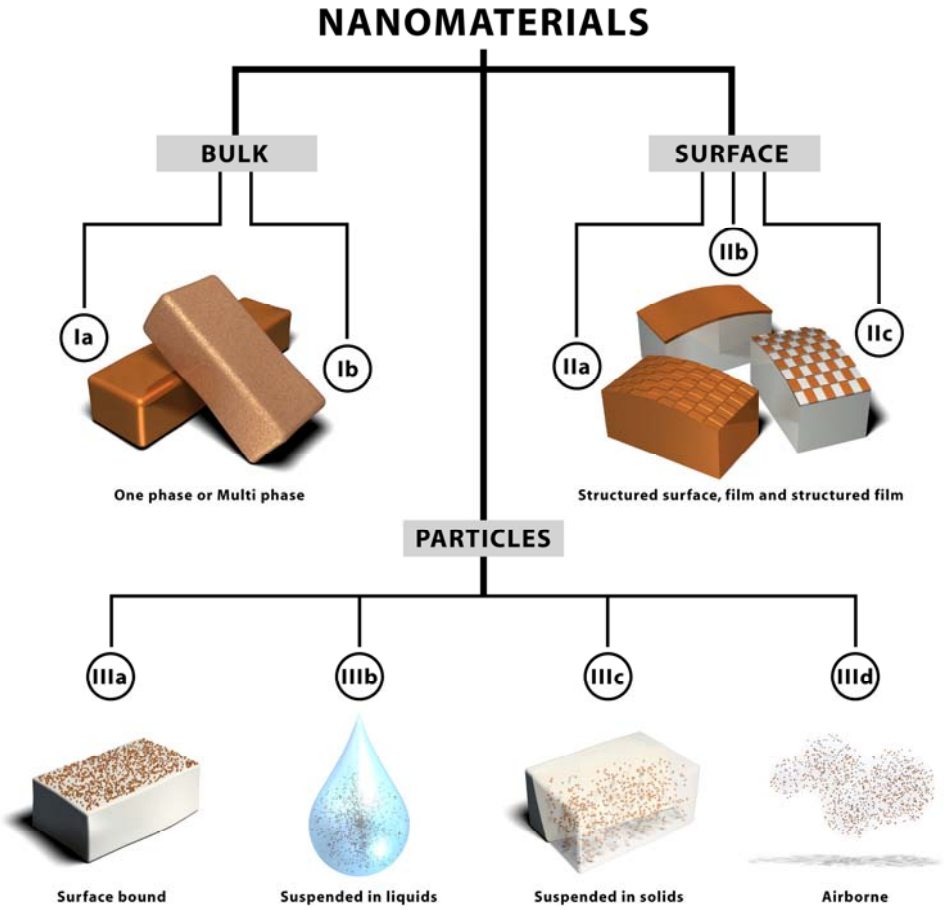

Figure 1. The categorization framework for nanomaterials. The nanomaterials are categorized according to the location of the nanostructure in the material (Reprinted from Hansen *et al.* 2007).

Guidance on how to determine the location of the nano-element can be found in Hansen ***et al.*** (2007) and Hansen ***et al.*** (2008). In short, Hansen ***et al.*** (2007) suggest categorizing nanomaterials depending on the location of the nanoscale structure in the system. This leads to a division of nanomaterials into three main categories:

1. materials that are nanostructured in the bulk;
2. materials that have nanostructure on the surface and;
3. materials that contain nanostructured particles.

As a general rule processes, products and technical functions which involve ‘‘nanoparticles suspended in liquids’’ or ‘‘airborne nanoparticles” exposure is to be expected. Hence these use categories have been given a color code of red (●). If they involve ‘‘surface-bound nanoparticles’’ and hence may cause exposure, a color code of yellow (●) has been given and finally, if they involve “nanoparticles suspended in solids” for which exposure is not expected they have been assigned a color code of green (●) (see Figure 2).

Although it seems unlikely, it should be recognized that there maybe some products for which the professional end-users or the users of NanoRiskCat do not know or cannot determine the location of the nano-element in the product and hence cannot determine the exposure potential. In such cases, the product would fall into the fourth category due to lack of information, with an associated grey color-code (●).

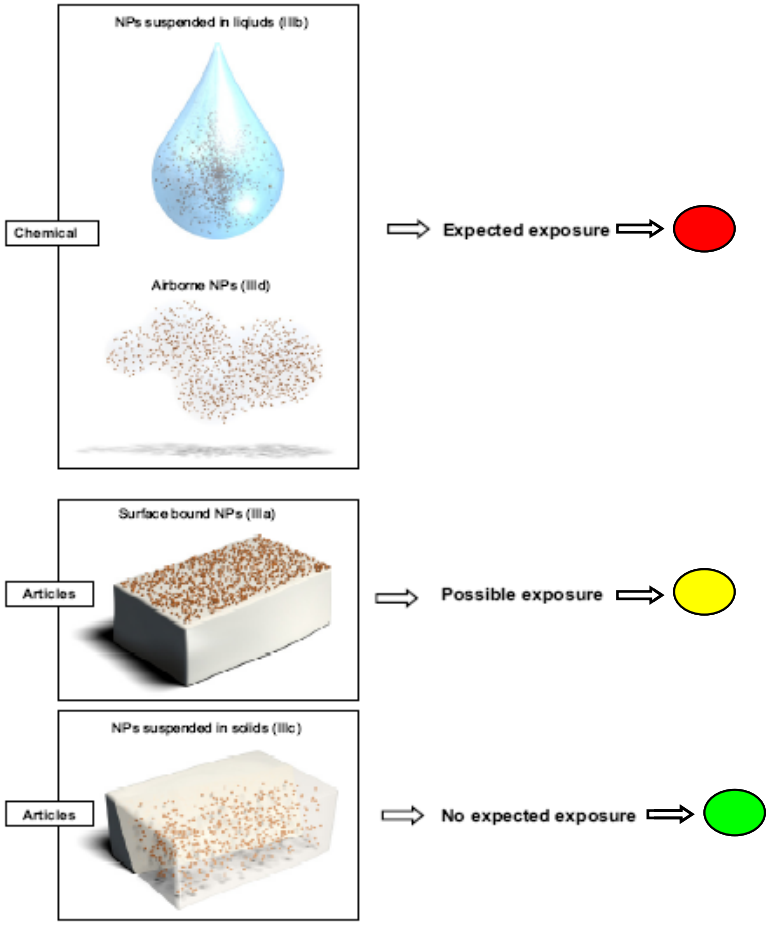

Figure 2. Generic approach used in NanoRiskCat to assign the color-code to products with no, possible and expected exposure depending on the location of the nanomaterial in the product (adapted from Hansen *et al.* 2008c)

3.2.1 Evaluating the potential exposure for professional end-users

The first part of the exposure evaluation in NanoRiskCat focuses on the evaluating the exposure potential for professional end-users of a nanomaterial containing product. Evaluating the exposure potential for workers in the production chain of nanomaterials is beyond the scope of this framework, but guidance on how to address this issue can be found in among other NANOSAFER (Industriens Branchearbejdsmiljøråd 2011) and in Genaidy ***et al.*** (2009).

The evaluation of the potential exposure for professional end-users is based on REACH Guidance on information requirements and chemical safety assessment Appendix R.12:

- 27 Process categories (PROC) e.g. PROC 1= Use in closed process, no likelihood of exposure (•), PROC 7= Industrial spraying (•), PROC 10= Roller application or brushing (•)
- 40 Chemical Product Categories (PC) e.g. PC 1= Adhesives, sealants (•) and PC 2= Adsorbents (•)
- 51 functional categories (FC) a substance may have in a chemical product or article e.g. FC 1= Aerosol propellants (•) and FC 4= Anti-freezing agents (•) (ECHA 2010)

This, for instance, leads to the color code of green being assigned to PROC 1 since in this process categories are defined by "Use in closed process, no likelihood of exposure". The color code of red is assigned to PROC 7 since the examples and explanations column states "Air dispersive techniques" and "Substances can be inhaled as aerosols". Applying this approach would mean for instance that Chemical Product Category called "Air care products" (PC 3) would be "red" since it is assumed that the nanomaterial will have to be suspended in liquids and/or may become airborne and hence exposure is to be expected. Finger paint (PC 9c) would also be classified as "red" since it is assumed that nanomaterials used in finger paint would have to be suspended in liquids and there is direct dermal exposure. It should be noted that personal protection equipment is not included in the consideration of the potential of worker exposure.

As the exposure potential is expected to vary over the course of the use phase of the product, only the highest exposure potential for professional end-users should be reported as the first dot in NanoRiskCat.

The color code assigned to the various PROCs, PCs and FCs should be used as the default colors that should be reported as the first dot in NanoRiskCat. Deviation of the default color assigned to each PROCs, PCs and FCs would have to be elaborated on and explained and justified in a reasonable and transparent manner by the user of NanoRiskCat. The list of PROCs, PCs and FCs are not meant to be regarded as a complete list and other uses should be described as appropriate and given a color code by the user of the NanoRiskCat with due explanation.

3.2.2 Evaluating the potential exposure for consumers

As in the case of professional end-users, the evaluation of the potential exposure for consumers is based on ECHA's REACH Guidance on information requirements and chemical safety assessment Appendix R.12:

- 40 Chemical Product Categories (PC), e.g. PC 1= Adhesives, sealants (•) and PC 2= Adsorbents (•)
- 13 Article categories (AC), no release intended (AC), e.g. AC 1= Vehicles (•)
- 8 Use descriptors for articles with intended release of substances, e.g. AC 31= Scented clothes (•)

As in the case of professional end-users a color code has been assigned to each use category (see Appendix 3) depending on the location of the nanomaterial and a judgment of the likelihood of consumer exposure of a given nanomaterials being used in a product or article that falls into each of these chemical product and article categories. This judgment is based partly on the description and explanation associated with each PC and AC and partly on an estimation of the exposure potential of the use of a given nanomaterial used in a product and/or article following the framework developed by Hansen ***et al.*** (2007, 2008).

As the exposure potential is expected to vary over the course of the use phase of the product, only the highest exposure potential for consumers should be reported as the second dot in NanoRiskCat.

This color code could then be the default color that should be reported as the second dot in NanoRiskCat. Deviation of the default color assigned to each Chemical Product Category would have to be elaborated on and explained and justified in a reasonable and transparent manner by the user of NanoRiskCat.

3.2.3 Evaluating the exposure for the environment

As in the case of professional end-users and consumers, evaluating the exposure for consumers is based on ECHA's REACH Guidance on information requirements and chemical safety assessment Appendix R.12:

- 13 Article categories (AC), no release intended (AC) e.g. AC 1= Vehicles (●)
- 8 Use descriptors for articles with intended release of substances e.g. AC 31= Scented clothes (●)
- 12 Environmental Release Categories (ERC) e.g. ERC 1= Manufacture of substances (●) , ERC 2= Formulation of preparations (●), and ERC 12b= Industrial processing of articles with abrasive techniques (high release) (●)

As in the case of professional end-users and consumers, a color code has been assigned to each Environmental Release Category (see Appendix 3.6) depending on the location of the nanomaterial and our judgment of the likelihood of environmental exposure of a given nanomaterial that falls into each of these categories. This judgment is based partly on the description and explanation associated with each PC and AC and partly on an estimation of the exposure potential of the use of a given nanomaterial used in a product and/or article following the framework developed by Hansen ***et al.*** (2007, 2008). Using this approach, ERC 1 would be assigned a color code of yellow whereas ECR 8D and ERC 10B would be assigned the color red.

As the exposure potential is expected to vary over the course of the use phase of the product, only the highest exposure potential for the environment should be reported as the third dot in NanoRiskCat. Deviation of the default color assigned to each category would have to explained and justified in a reasonable and transparent manner by the user of NanoRiskCat. There are furthermore a few ERC (i.e. ERC 4 and ERC 6a) for which a default color code could not be assigned and in such cases it is up to the user of NRC to assign the most appropriate color code to their uses.

3.3 Criteria for evaluating the potential human health hazards

The tiered approach was developed to assign a color to the human health hazards to a given nanomaterial as illustrated in Figure 3. When assigning a color to the dot representing potential human health hazards (dot number four) of a given nanomaterial the following indicators/qualifiers should be considered:

1. Does the ***nanomaterial*** fulfil the HARN[7] paradigm?

[7] HARN refers to High Aspect Ratio Nanoparticles indicating that the nanoparticles have a length to diameter aspect ratio greater than 10 to 1. Furthermore, it is required that: 1) The diameter of the fibres must be thin enough pass ciliated airways; 2) the

2. Is the ***bulk form*** of the nanomaterial known to cause or may cause serious damaging effects, i.e. is the bulk form classified according to the CLP[8] with regard to one or more serious health hazards such as germ cell mutagenicity, carcinogenicity or reproductive toxicity in category 1A, 1B or 2?

3. Is the ***bulk form*** of the nanomaterial classified for other less severe adverse effects according to the CLP such as skin corrosion/irritation category 2 and specific target organ toxicity-single exposure category 3?

4. Is the specific ***nanomaterial*** known to be acute toxic?

5. Are there indications that the ***nanomaterial*** causes genotoxic, mutagenic, carcinogenic, respiratory, cardiovascular neurotoxic or reproductive effects in humans and/or laboratory animals or has organ-specific accumulation been documented?

The background for each of these criteria will be explained and elaborated on in the following section. For each of these questions, reasoning should be provided with proper referencing to the scientific and/or non-scientific literature and an answer of each of the question should be provided in the form of either: yes, maybe, no, or no information. The answer "yes" implies that there is conclusive evidence or data giving cause to substantial concern that the nanomaterial in question may cause ir-/reversible effects (e.g. carcinogenicity) or that the nanomaterial holds a given property (e.g. persistency). "Maybe" indicates that data is not conclusive but gives cause to some concern, whereas "no" indicates that there is conclusive evidence that indicates that the nanomaterial does not cause adverse ir-/reversible effects and/or hold the properties in question. No data indicates that no or very limited and insufficient data is available for hazard evaluation.

While in principle none of these questions are more important than others, Figure 3 gives a guidance on the order in which they may be evaluated and a short description of the criteria to be used. Below follows a more detailed description of each indicator and the cut-off values chosen.

The red color code in Figure 3 signifies that indications of adverse effects are high; the yellow signifies that indications of adverse effects are medium, and green that indications of adverse effects are low. Grey should be used if there are numerous data gaps and unknowns to warrant no conclusion to be made about the human hazards of the nanomaterial. Transparency in the assigning of a color code is key and very important. Therefore, all categorizations made based on Figure 3 must be accompanied by an explanatory text on how the conclusion was reached (as shown in the cases in Chapter 4).

NanoRiskCat is a tiered approach in the sense that once a color code has been

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length must be long enough to initiate the onset of e.g. frustrated phagocytosis and other inflammatory pathways; and 3) the nanomaterials must be biopersistent (Tran ***et al.*** 2008).

[8] Regulation (EC) No 1272/2008 of the European Parliament and of the Councul of 16 December 2008 on classification, labelling and packaging of substances and mixtures, amending and repealing Directives 67/548/EEC and 1999/45/EC, and amending Regulation (EC) No 1907/2006

triggered (e.g. bulk materials CLP classified as an Acute toxic category 3 after oral exposure would trigger “red”), the nanomaterial cannot obtain a different color code (yellow, green or grey) even though the oral LC_{50} might be > 300 mg/l but 2000 mg/kg bodyweight.

It should be noted that the classification according to the Regulation (EC) No 1272/2008 on classification, labelling and packaging of substances and mixtures for the bulk material is used in the human hazard categorization in NanoRiskCat (EP and CEU 2008).

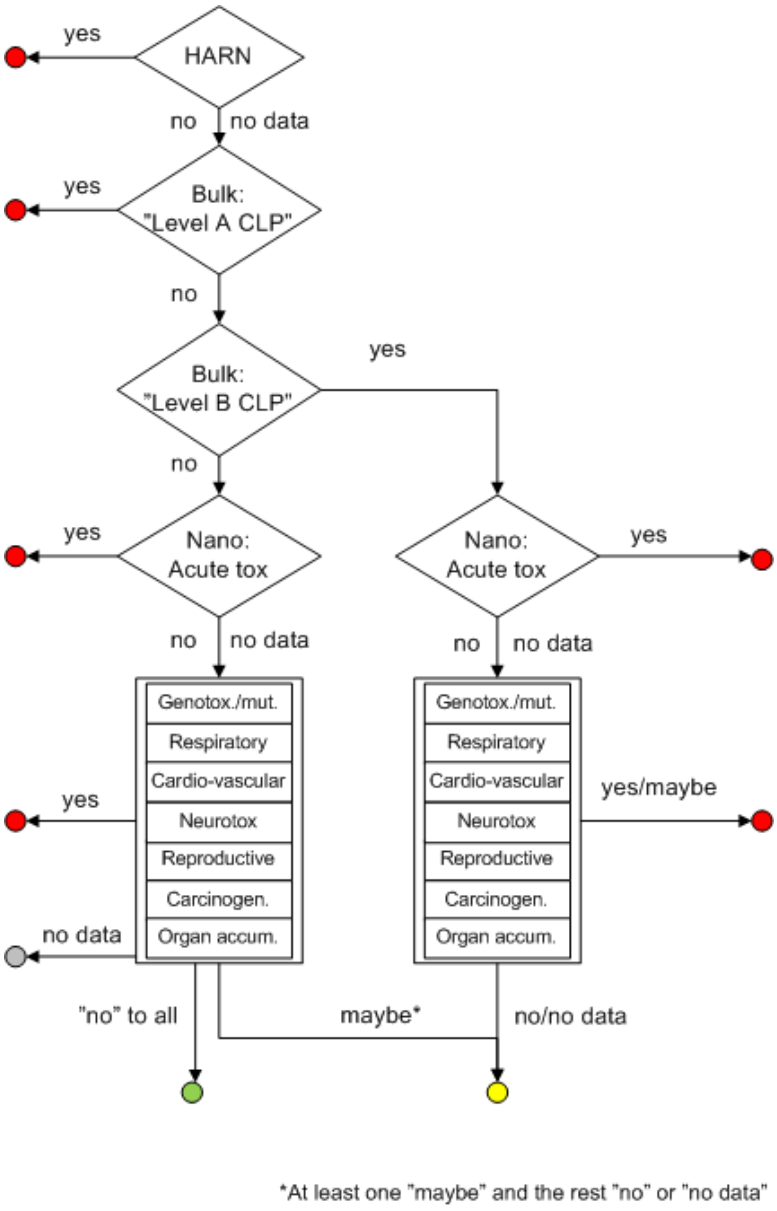

Figure 3. Road-map for assigning a human hazard colour code in NanoRiskCat. Red, yellow and green indicate high, medium and low indication of effect whereas grey indicates too limited data to make an assessment. For a guide to answering the questions, please refer to section 3.3.1 to 3.3.6.

3.3.1 HARN: Does the nanomaterial fulfill the HARN paradigm?

There is evidence that longer, durable or biopersistent fibres are more toxic by mass than shorter fibres of the same composition when inhaled. Animal studies suggests that fibres < 5 µm in length pose little risk of disease development, whereas 8 - 10 µm long fibers can cause mesothelioma and 10 - 15 µm produce disease in the lungs. (Meldrum 1996). The World Health Organization

has defined a fiber as being a particle of a length >5 µm, and a diameter <3 µm, and with an aspect ratio (length to diameter) of >3:1 (Meldrum 1996, BSI 2007).

In regard to nanomaterials specifically the so-called HARN-paradigm as been proposed by Tran ***et al.*** (2008). HARN refers to High Aspect Ratio Nanoparticles. In order to be classified as HARN the nanomaterials must have a high surface area and a length to diameter aspect ratio greater than 10 to 1. Furthermore, it is required that: 1) The diameter of the fibres must be thin enough pass ciliated airways; 2) the length must be long enough to initiate the onset of e.g. frustrated phagocytosis[9] and other inflammatory pathways; and 3) the nanomaterials must be biopersistent. Nanomaterials that would typically fulfil this paradigm would be e.g. carbon nanotubes, nanofibers, nanowires and nanorods (Tran ***et al.*** 2008). As shown in figure 3, an HARN classification will lead to a red color coding.

3.3.2 Bulk – "Level A CLP": Is the bulk form of the nanomaterial known to cause or may cause serious damaging effects?

The second question relates to the hazard characteristics of the bulk or parent version of a nanomaterial and if it is already CLP classified in regard to:

a) acute toxicity
b) skin corrosion
c) skin irritation
d) serious eye damage/irritation
e) respiratory and skin sensitization
f) germ cell mutagenicity
g) carcinogenicity
h) reproductive toxicity
i) specific target organ toxicity - single exposure
j) specific target organ toxicity - repeated exposure and
k) aspiration toxicity

This enables a broad identification of potential hazard (and a form of read-across) from a previously identified hazard associated with the material. In case the answer is "yes" a red color coding will be triggered if the CLP classification is one of the following:

1. Acute toxicity category 1-4
2. Germ cell mutagenicity category 1A, 1B or 2
3. Carcinogenicity category 1A, 1B or 2
4. Reproductive toxicity category 1 A, 1B or 2
5. Specific target organ toxicity - single exposure category 1 or 2
6. Specific target organ toxicity - repeated exposure and category 1 or 2
7. Aspiration toxicity category 1
8. Skin corrosion/irritation category 1A, 1B or 1C
9. Serious eye damage/irritation category 1
10. Respiratory and skin sensitization category 1

[9] Phagocyte failing to engulf its target whereby toxic agents from inside the phagolysosome can be released causing damage to healthy cells and tissue (Wikipedia 2011)

These classifications are termed “Level A CLP classifications”. The categorization of these CLP classifications as Level A is based on the CLP description of these hazard categories. For a substance or material to get one or more of the Level A CLP classifications they have to be either known or strongly suspected to cause severe and potentially irreversible harm.

In the case there is no CLP Level A classification association with the bulk form of the material, the answer to this question would be “no”, which again would trigger the need to go to the next step in the flow diagram in Figure 3. In case a nanomaterial does not have a bulk parent material (e.g. fullerene, nanotubes and organoclays) the answer to this question should be “no” by default.

3.3.3 Bulk – “Level B CLP”: Is the bulk form of the nanomaterial classified for other less severe adverse effects according to the CLP?

The third question again relates to the hazard characteristics of the bulk or parent version of a nanomaterial and whether it is suspected of causing one or more specific health hazards i.e. if the CLP classification is one of the following:

1. Skin corrosion/irritation category 2
2. Specific target organ toxicity-single exposure category 3
3. Serious eye damage/irritation category 2

These classifications are termed “Level B CLP classifications” and are considered to be less severe that Level A CLP classifications. The reasons that these CLP classifications are considered less severe is that the effects are described as reversible in the CLP hazard categories.

In case the answer is “yes”, the nanomaterials in questions can no longer be classified as “green”. In case a nanomaterial does not have a bulk form (e.g. fullerene, carbon nanotubes and organoclays), only the question about documented nano-specific effects has to be addressed.

3.3.4 Nano – Acute tox: Is the nanoform of the materials known to be acute toxic?

This question focuses specifically on what is known about the acute toxicity of the nanoform of the material. Acute toxicity is defined as adverse effects resulting from an oral or dermal administration of a single dose or multiple doses within 24 hours to a nanomaterial or an inhalation exposure of 4 hours (ECHA 2008, United Nations 2009).

Adverse effects could be clinical signs of toxicity, abnormal body weight changes, and/or pathological changes in organs and tissues, which in some cases may be lethal. Local irritation or corrosion of the gastro-intestinal tract, skin or respiratory tract following a single exposure are included here as well and the same goes for cellular level acute toxicity such as (i) general basal cytotoxicity (ii) selective cytotoxicity and (iii) cell-specific function toxicity (ECHA 2008).

As shown in Figure 3, a nanomaterial with a known acute toxicity will trigger a red color coding. The cut-off values chosen to determine the toxicity of a nanomaterial are similar to the acute toxicity hazard category 4 in CLP (EP and CEU 2008). For oral and dermal acute toxicity estimates (based on LD_{50}/LC_{50} when available), the acute toxicity cut-off has been chosen to be 2000 mg/kg. For dusts and mists (solid particles and liquid droplets in a gas) the acute toxicity estimate cut-off has been set to 5 mg/kg.

3.3.5 Are there indications that the nanomaterial causes genotoxic-, mutagenic, carcinogenic, respiratory, cardiovascular, neurotoxic or reproductive effects in humans and/or laboratory animals or has organ-specific accumulation been documented?

Question 5 focuses specifically on whether there are indications that the nanomaterial may cause either mutagenic, genotoxic, carcinogenic, respiratory, cardiovascular, neurotoxic or reprotoxic effects in humans and/or laboratory animals and whether organ-specific accumulation of nanomaterials have been documented.

As summarized in Stone ***et al.*** 2009 and Hougaard ***et al.*** (2010), there is compelling evidence that some nanoparticles may be associated with one or more of these end-points. Due to their severity, a response significantly over background in any of these endpoints results in a “red” classification.

For each of these endpoints, the user of NanoRiskCat has to review the literature and answer “yes”, “no” or “maybe” e.g. yes, there are indications that the nanomateirals is genotoxic.

Providing rigid rules for how to interpret the scientific evidence is not very meaningful, but as a general rule the answer would be "yes" if there are indications from epidemiological- and/or ***in vivo*** studies that indicate or confirm one or more of these effects.

In case of conflicting evidence from epidemiological- and/or in vivo studies, the answer to Question 5 could still be “yes” if there are one or more reasonable explanations for why one of the studies did or did not observed an adverse effect. The answer could similarly be “no” if there are one or more reasonable explanations (e.g. confounders) for why a study did observe an adverse effect while others did not. Finally, the answer would be “maybe” in cases where there is conflicting evidence and no reasonable explanations for why studies differ.

In regard to ***in vitro*** testing, it has been shown that these studies may not always accurately predict potential hazards of nanomaterials in more complex biological environments (CCA 2008) and hence indications of one or more adverse effects should be used either to discuss mechanisms of toxicity or in conjunction with other lines of evidence. In case no other lines of evidence are available, results stemming from ***in vitro*** can only be used to answer “maybe”, as positive or negative indications of effects are not considered convincing enough to answer “yes” or “no” at this point in time.

In case that the bulk form has no CLP classification and the answer is “no” to each for these effects, this would trigger a categorization as “green” whereas it would be “yellow” if the answer is “maybe” to at least one of the endpoints.

The alternate case is if the bulk form of the nanomaterial has a classified as a:

- Skin corrosion/irritation CLP category 2
- Specific target organ toxicity-single exposure CLP category 3
- Serious eye damage/irritation CLP category 2

In this case the fact that there are indicators that the nanomaterial might be associated with one or more nanospecific adverse effects as well would lead to classification as “red”. In case the bulk form has a level B CLP classification and there are no nanospecific adverse effects associated to it, would lead a classification as “yellow”.

In the case that no conclusion can be reached in regard to any of these effects, no categorization of the nanomaterial can be made this would lead a classification as “grey”.

3.3.6 Standard sentences associated with human health hazard classification as red, yellow and grey

To help communicate the scientific reasoning behind assigning a human health hazard classification and why a given nanomaterial was assigned red, yellow or grey, a number of standard sentences have been developed. These standard sentences are meant to reflect primarily whether the conclusion has been reached based on classification of the bulk form of the materials and/or ***in vivo*** or ***in vitro*** data on the nanomaterial and in regard to what endpoint. Depending to the final classification in regard to human health, the user of NRC has to select one or more of those sentences that best reflect the scientific basis for assigning the color code. A list of these sentences is given in Appendix 2, Table A2.1.

3.4 Criteria for evaluating the environmental hazard profile

In order to provide an initial estimate of the environmental hazards related to a given nanomaterial and its application and what is already known about the bulk form of the material, the following indicators/qualifiers should be considered:

1. Is the nanomaterial in question reported to be hazardous to environmental species?
2. Is the nanomaterial in question persistent?
3. Is the nanomaterial in question bioaccumulative?
4. Could use of the nanomaterial in question lead to potentially irreversible harm to the environment (e.g. ecosystem effects)?
5. Is the nanomaterial in question readily dispersed?
6. Is the nanomaterial in question novel?

For each of these questions, reasoning should be provided with proper referencing to the scientific and/or non-scientific literature and an answer of each of the question should be provided in the form of either: yes, maybe, no, or no information. The answer “yes” implies that there is conclusive evidence or

data giving substantial concern that the nanomaterial in question may cause ir-/reversible effects (e.g. mortality) or holds a given property (e.g. persistency). “Maybe” indicates that data is not conclusive but gives some concern for the effects in question, whereas “no” indicates that there is conclusive evidence that indicates that the nanomaterial does not cause adverse ir-/reversible effects and/or hold the properties in question. No data indicates that no or very limited and insufficient data is available for hazard evaluation. In principle none of these indicators are more important than others. As in the case of human health, Figure 4 gives guidance on the order in which they may be evaluated.

Short descriptions of the criteria to be used are given in sections 3.4.1-3.4.9. Outset is taken in existing criteria for chemicals with due consideration to the uncertainty related to ecotoxicological hazard of nanomaterials e.g. by changing the cut-off values for LC_{50} or EC_{50}. Below follows a more detailed description of each indicator and the cut-off values chosen. It should also be noted that the classification according to the European Regulation on classification, labelling and packaging of substances and mixtures (EP & CEU 2008) for the bulk material is used in the environmental hazard categorization in NanoRiskCat.

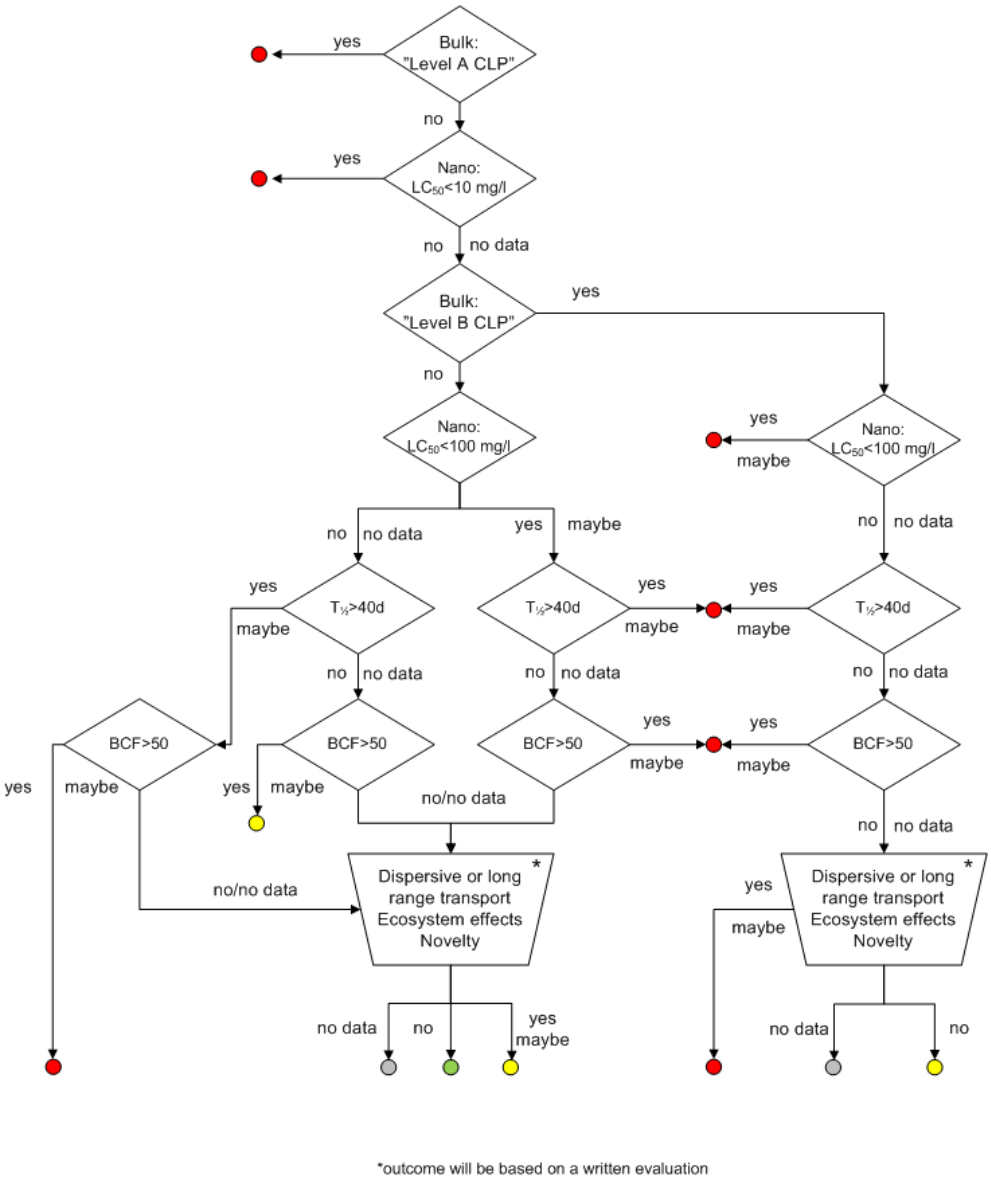

Figure 4. Road-map for assigning an environmental hazard colour code in NanoRiskCat. Red, yellow and green indicate high, medium and low indication of effect whereas grey indicates too limited data to assess effect. For a guide to answering the questions, please refer to sections 3.3.1 to 3.3.9.

It is important to note that NanoRiskCat is a tiered approach in the sense that once a color code has been triggered (e.g. bulk materials CLP classified as Chronic 1 which would trigger "red") the nanomaterial cannot get a different color code (yellow, green or grey) even though the (LC_{50} or EC_{50}) might > 100 mg/l and the half-life might be < 40 days and the BCF < 50.

3.4.1 Bulk – "Level A CLP": Is the bulk form of the nanomaterial classified as CLP Acute 1 or Chronic 1 or Chronic 2?

The first question relates to the hazard characteristics of the bulk or parent version of a nanomaterial and if it is already classified as an Acute 1 or Chronic 1 and Chronic 2. This enables a broad identification of potential hazard (and a form of read-across) from a previously identified hazard associated with the material. In case a nanomaterial does not have a bulk parent material

(e.g. carbon nanotubes and quantum dots) the answer to this question should be no by default.

3.4.2 Nano – LC_{50}<10 mg/l: Is the nanomaterial in question reported to be hazardous to environmental species i.e. LC_{50} or EC_{50} <10 mg/l?

The second question is whether the nanomaterial in question reported to be hazardous to environmental species i.e. LC_{50} or EC_{50} <10 mg/l? Data from the base-set of organisms traditionally used for chemical risk assessment and labelling (i.e. fish, crustacean, and algae) will be given the highest rank. As shown in Figure 4, LC_{50}-values or EC_{50}-values from tests of nanomaterials with base-set organisms below 10 mg/l will lead to a red color coding. Values below 10 mg/l will traditionally be referred to as either toxic (1-10 mg/l) or very toxic (< 1 mg/l) to aquatic organisms. Focus is directed towards well-established endpoints like EC_{50}, NOEC- (No Observed Effect Concentration) and LOEC (Lowest Observed Effect Concentration)-values, but all available ecotoxicity data should be taken into account. The reason for assigning a red color code to materials with LC_{50}- or EC_{50}-values below 10 mg/l is the presently ongoing discussion on which dose-metrics will be the best to use in nano-ecotoxicology. The user of NanoRiskCat should be aware of this rather controversial discussion and may decide to follow a precautionary path, preventing false-positive results (i.e., claiming that a material is not harmful, while in fact it is).

3.4.3 Bulk – "Level B CLP": Is the bulk form of the nanomaterial classified as CLP Chronic 3 or Chronic 4 or documented nano-specifc effects?

The third question relates to whether the bulk material classified as CLP Chronic 3 or Chronic 4 or whether there are documented nano-specific effects. In case the answer is "yes", this rules out the possibility of the nanomaterials in questions being classified as "green". In case a nanomaterial does not have a bulk parent material (e.g. carbon nanotubes and quantum dots) only the questions about documented nanospecific effects have to be addressed. This may apply to cases where statistically significant effects of nanomaterials have been observed, but EC_{50} or LC_{50} values cannot be established or non-standardized endpoints have been applied.

3.4.4 Nano – LC_{50}<100 mg/l: Is the nanomaterial in question reported to be hazardous to environmental species i.e. LC_{50} or EC_{50} <100 mg/l?

This question addresses whether the nanomaterial in question has been reported to be hazardous to environmental species i.e. LC_{50} or EC_{50} <100 mg/l? Data from the base-set of organisms traditionally used for chemical risk assessment and labelling (i.e. fish, crustacean, and algae) will be given the highest rank. As shown in Figure 4, LC_{50}-values or EC_{50}-values from tests of nanomaterials with base-set organisms below 100 mg/l will either lead to a red color coding or a subsequent evaluation of persistency and bioaccumulation potential. The value of 100 mg/l is chosen in accordance to the CLP cut-off values for environmental hazards. Focus is directed towards well-established endpoints like EC_{50}-, NOEC- and LOEC-values, but all available ecotoxicity data should be taken into account.

3.4.5 $T_{½}$>40 days: Is the nanomaterial in question persistent?

The fifth question regards the persistency of the nanomaterial. In NanoRisk-Cat a nanomaterial is considered persistent if freshwater tests reveal a degradation half-life greater than 40 days. If the nanomaterial is carbon-based, tests performed in accordance with the OECD test hierarchy for degradability (OECD 2011) will have the highest rank, but other degradation studies carried out in environmental matrices will also be taken into account in the evaluation. This means that positive results in OECD 301 tests for ready biodegradability (OECD 1992) will result in a "not persistent" categorization. The same goes for positive results of tests for inherent biodegradability (i.e. >70% mineralization) performed in accordance with OECD test guidelines. If <20% mineralization is reached within the incubation period for OECD tests for inherent biodegradability, the materials may be regarded as persistent. In cases where no or insufficient information from OECD tests is available, REACH criteria for persistency will be applied. This means that a material is considered persistent if freshwater tests reveal a degradation half-life greater than 40 days (T½> 40 days in freshwater).

For inorganic nanomaterials the term persistency is not well-defined. On the one hand inorganic nanomaterials can be claimed to be persistent per se since the elements cannot be degraded. In this way all inorganic nanomaterials will be classified as persistent, but attention should be given to the fact that some nanomaterials may be reactive (e.g. nano-scale zero-valent iron that may be oxidized to iron-oxides, or nano-silver that may dissociate to silver-ions) and therefore be transformed to other materials or other forms of the same element. This "new" forms may or may not be nano-scaled. Thus, the recommendation is that non-reactive inorganic nanomaterials are given the classification "persistent" whereas reactive inorganic nanomaterials are classified as "maybe persistent". It is recommended not to use the term "non-persistent" for inorganic nanomaterials.

3.4.6 BCF>50: Is the nanomaterial in question bioaccumulative i.e. BCF>50?

The criterion for classifying a chemical as bioaccumulative according to the REACH guidance is that the bioconcentration exceeds the value of 500. This indicates that the concentration in the organism is 500 times higher than the concentration in the surrounding environment (or that the uptake rate in organisms is 500 times higher than the depuration rate). In NanoRiskCat a cut-off value of 50 is recommended. This value is chosen on a precautionary basis acknowledging that 1) analytical techniques for quantification of nanomaterials in both environmental media and biological tissues are not yet fully developed, and 2) that accumulation of nanomaterials may not be defined by total body burden, but more likely by a differential uptake and perhaps translocation to specific organs. The latter type of behaviour is not comparable to what is known for the dissolved organic chemicals for which the bioconcentration cut-off values originally were defined in the REACH guidance. Nanomaterials will in most cases not be dissolved in the test media, but (at best) be stable suspensions of particles.

Traditionally, an evaluation of the potential for bioaccumulation for organic chemicals is done based on the octanol-water partitioning coefficient (K_{ow}). However, this approach is not considered valid for nanomaterials (Baun ***et al.*** 2009). Therefore, an evaluation of bioaccumulation potential for both organic

and inorganic nanomaterials need to be based on actual measured data either from laboratory or field studies.

3.4.7 Dispersive or long-range transport, ecosystem effects and novelty

As indicated in Figure 4 considerations on the transport, ecosystem effects and novelty should be included as the final step. The outcome of these considerations is a written evaluation aimed at answering "yes", "maybe", "no" or "no data".

The first question to be considered is: Is the nanomaterial dispersive?
Although not something that is normally considered in the environmental hazard categorization, there is historical evidence that the mere fact that a substance or material is disperse in the environment is a good indicator of potential harm that has yet to become discovered (EEA 2001). In relation to this, data on the substance's volatility, solubility and mobility in (e.g. soil) would be of relevance for a "regular" organic chemical, but for nanomaterials, the volatility should be disregarded. The mobility in soil can only be evaluated on actual data measuring the distribution, since no estimation equations have been established for the time being.

The second question to be considered is: Could use of the nanomaterial in question lead to potentially irreversible harm to the environment (e.g. ecosystem effects)?
In the case that a nanomaterial does not fulfil any of the criteria above, a series of broader questions and elements need to be taken in consideration. The first question is whether there are documented or potential ecosystem effects (e.g. through oxygen depletion, effects on nutrient balance, shifts in populations), but also effects on global scale like ozone depletion, or global warming potential.

The final question to be considered is: Are we dealing with a novel material?
Although not something that is normally considered in the environmental hazard categorization, there is historical evidence that the mere fact that a substance or material is novel is a good indicator of potential harm that has yet to become discovered (EEA 2001). No single exhaustive taxonomy exists for novel materials and as noted by Royal Commission on Environmental Pollution (2008) it is unlikely that one is possible or even necessarily desirable. However still, the UK Royal Commission on Environmental Pollution (2008) distinguished between four types of novel materials:

1. new materials hitherto unused or rarely used on an industrial scale;

2. new forms of existing materials with characteristics that differ significantly from familiar or naturally-occurring forms, e.g. silver and gold;

3. new applications for existing materials or existing technological products formulated in a new way, e.g. cerium oxide used as a fuel additive;

4. new pathways and destinations for familiar materials that may enter the environment in forms different from their manufacture and envisaged use (RCEP 2008).

Novel would in this case be defined as materials that humans and environment have not previously been exposed to any significant extent.

3.4.8 Standard sentences associated with environmental hazard classification as red, yellow and grey

To help communicate the scientific reasoning behind assigning an environmental hazard classification and why a given nanomaterial was assigned red, yellow or grey, a number of standard sentences have been developed. Depending on the final classification in regard to environmental hazards, the user of NRC can select one or more of those sentences that best reflect the scientific basis for assigning the color code. A list of these additional sentences is given in Appendix 2, Table A2.2.

4. NanoRiskCat applied in cases

In the following NanoRiskCat is applied on two case studies to serve as examples of how NanoRiskCat could be applied and to assist in the further development of the concept. They involve realistic uses of C_{60} and TiO_2 in products available for professional and non-professional users. While all data are realistic, the product names are constructed. NanoRiskCat is applied to the product by using the guidance provided in Chapter 3 as well as the generic template available in Appendix 1, the additional sentences for explaining color codes in Appendix 2 as well as the defaults colors assigned to various REACH Use Descriptor Categories in Appendix 3.

These two cases illustrate an "expert level" use of NanoRiskCat. This means that a literature review of primary scientific papers form the basis for filling in the NRC template provided in Appendix 1. It is very important that the user uses the NRC template in Appendix 1 for assigning the colors in order to maintain transparency in how the final conclusions were reached.

4.1 Case study 1: C_{60} in lubricant

The following case study is an example of how one could use NanoRiskCat on C60 used in lubricants. The case is based on a realistic use of C60 in a product available for professional and non-professional users. While real data is used, the product name is constructed. NanoRiskCat is applied to this product by filling out the information being asked for in the NRC template available in appendix 1 by using the guidance provided in chapter 3 as well as the series of tables available in Appendix 3 and the additional sentences for explaining color codes in Appendix 2.

NanoRiskCat

Subject: C60 in lubricant "C60 LuBExtreme" produced by Ex-LuB

Nanomaterial description	
Material source or producer:	Carlfullerene Proc.
Manufacturing process:	Arc method
Appearance:	Black powder
Chemical composition:	C60
Physical form/shape:	Powder/spherical
Purity:	99.5%
Size distribution:	~ 1 nm
Solubility:	1.3×10^{-11} mg/mL
State of aggregation or agglomeration:	No information
CAS number (if applicable):	99685-96-8
Product description	
C60 LuBExtreme is a liquid consisting of about 90% base oil and less than 10% additives. Soot-containing C_{60} (up to 1 % in the final product) is mixed together with other chemical additives in order to improve the sliding between metallic surfaces and thereby enhances the performance of the lubricant. The fullerenes molecules work as micro ball-bearings along sliding surfaces.	
Applications	
C60 LuBExtreme is to be used in the form of motor oil to protect the internal combustion engines in motor vehicles and powered equipment. The amount of C60 LuBExtreme needed at each oil shift will depend on the motor engine, but can easily range from 3-6 litres. C60 LuBExtreme is believed to last for minimum 10,000 km and maximum up to 15,000 km. Oil change is recommended after max. 6 months. In order to reduce and to prevent accidents, strict personal and industrial hygiene rules should be respected and contact with the body should be avoided through the use of: oil proof gloves, wearing of clothes with an efficient protection, no wearing of oil contaminated clothes, use of protection cream and no use of solvents, such as petroleum, petrol to remove oil from the skin. Inhalation of oil mists and fumes is possible and efficient ventilation must be installed. The acceptable limit for an oil mist is 1 mg/cm3 (The Danish Working Environment Authority 2002). Wearing goggles is recommended when oil spattering in the eyes are likely to occur.	

Exposure potential for professional end-users

According to table 4 in chapter 3 of the **NanoRiskCat** main report on Criteria for evaluating the exposure profile, the following REACH Use Descriptor Categories are relevant for C60 LuBExtreme.

REACH Cat.	#	Description	**Examples and explanations**
PROC	18	Greasing at high energy conditions	Use as lubricant where significant energy or temperature is applied between the substance and the moving parts
PC	24	Lubricants, greases, release products	
FC		Lubricants and lubricant additives	Substances entrained between two surfaces and thereby used to reduce friction: oils; fats; waxes; friction reducing additives

Exposures to the professional end-user of C60 LuBExtreme are multiple and to be expected. The main risk of direct contact with the C60 LuBExtreme is likely to be skin, eyes, but also airways potentially droplets from splashing and spills. Consequently the skin, eyes, air-ways and GI-tract (through inhalation and hand-to-mouth) are potential exposure routes. The frequency of exposure may be highly depending on profession. Considering the color-codes of the PROC(●), PC (●) and FC (●), we concluded that the overall

Exposure potential for professional end-users is ●

Consumer exposure potential

According to table 4 in chapter 3 of the **NanoRiskCat** main report on Criteria for evaluating the exposure profile, the following REACH Use Descriptor Categories are relevant for C60 LuBExtreme.

REACH Cat.	#	Description	**Examples and explanations**
PC	24	Lubricants, greases, release products	
AC, no intented release		Not applicable	
AC, intented release		Not applicable	

Consumer exposure of C60 LuBExtreme is multiple and to be during filling of oil lubricant. The main risk of direct contact with the C60 LuBExtreme is likely to be skin, eyes, but also airways for fumes and potentially droplets from splashing and spills. Consequently the skin, eyes, air-ways and GI-tract (through inhalation and hand-to-mouth) are potential exposure routes. The frequency of exposure is considered rare. Moreover, the consumer use is presumable by far dominated by oil-filling of relatively low-energy engines.

Considering the color-codes of the PC24 (●) and the non-applicability of AC, we concluded that the overall

Consumer exposure potential is ●

Environmental exposure potential

According to table 4 in chapter 3 of the **NanoRiskCat** main report on Criteria for evaluating the exposure profile, the following REACH Use Descriptor Categories are relevant for C60 LuBExtreme.

REACH Cat.	#	Description	**Examples and explanations**
AC, no intented release		Not applicable	
AC, intented		Not applicable	

release			
ERC	2	Formulation of preparations*	Mixing and blending of substances into (chemical) preparations in all types of formulating industries, such as paints and do-it-yourself products, pigment paste, fuels, household products (cleaning products), lubricants, etc.
ERC	4	Industrial use of processing aids in processes and products, not becoming part of articles	Industrial use of processing aids in continuous processes or batch processes applying dedicated or multi-purpose equipment, either technically controlled or operated by manual interventions. For example, solvents used in chemical reactions or the 'use' of solvents during the application of paints, lubricants in metal working fluids, anti-set off agents in polymer moulding/casting.
ERC	7	Industrial use of substances in closed systems	Industrial use of substances in closed systems. Use in closed equipment, such as the use of liquids in hydraulic systems, cooling liquids in refrigerators and lubricants in engines and dielectric fluids in electric transformers and oil in heat exchangers. No intended contact between functional fluids and products foreseen, and thus low emissions via waste water and waste air to be expected.
ERC	8a	Wide dispersive indoor use of processing aids in open systems	Indoor use of processing aids by the public at large or professional use. Use (usually) results in direct release into the environment/sewage system, for example, detergents in fabric washing, machine wash liquids and lavatory cleaners, automotive and bicycle care products (polishes, lubricants, deicers), solvents in paints and adhesives or fragrances and aerosol propellants in air fresheners.
ERC	8d	Wide dispersive outdoor use of processing aids in open systems	Outdoor use of processing aids by the public at large or professional use. Use (usually) results in direct release into the environment, for example, automotive and bicycle care products (polishes, lubricants, deicers, detergents), solvents in paints and adhesives.

ERC	9b	Wide dispersive outdoor use of substances in closed systems	Outdoor use of substances by the public at large or professional (small scale) use in closed systems. Use in closed equipment, such as the use of hydraulic liquids in automotive suspension, lubricants in motor oil and break fluids in automotive brake systems.

A number of environmental releases of C60 LuBExtreme can be foreseen in the short- and the long-term. C60 might be combusted if oil enters the engine during use or they may be removed together with the oil if they remain suspended in the liquid phase when the oil is changed. Unintended direct release occurring from leaks, spills or sublimation of fullerenes also has to be expected and finally, C60 may adhere to metallic components of the car and will eventually be incorporated in the end-of-life vehicle engine. Environmental exposure during waste handling is possible.

The number of Environmental Release Categories that might be relevant for C60 LuBExtreme is multiple, however a number of the ERCs listed are considered not to be relevant since these are indoor industrial uses and hence fall outside the scope of **NanoRiskCat**. This is the case of ERC 2, 4 and 7.

Considering the color-codes of the ERC 8d (●) and ERC (●) and the non-applicability of AC and ERC 2 (●), ERC4 (●) and ERC7 (●), we concluded that the overall

Environmental exposure potential is ●

Literature methodology/sources of information

Three review articles were primarily used as sources of information to fill out the NanoRiskCat●●●|●● for C60,but where relevant a number of scientific articles were used and cited:

Review articles:

1. Stone V, Hankin S, Aitken R, Aschberger K, Baun A, Christensen F, Fernandes T, Hansen SF, Hartmann NB, Hutchinson G, Johnston H, Micheletti G, Peters S, Ross B, Sokull-Kluettgen B, Stark D, Tran L. 2009. Engineered Nanoparticles: Review of Health and Environmental Safety (ENRHES). Available: http://nmi.jrc.ec.europa.eu/project/ENRHES.htm (Accessed July 15, 2010)
2. Shinohara, N., Nakamishi, J., Gamo, M. 2009. Risk Assessment of Manufactured Nanomaterials – C60. Available: http://www.aist-riss.jp/main/modules/product/nano_rad.html?ml_lang=en (Accessed July 15, 2010)
3. Nielsen GD, Roursgaard M, Jensen KA, Poulsen, SS, Larsen ST. In vivo biology and toxicology of fullerenes and their derivatives. Basic Clin Pharmacol Toxicol 2008;103(3):197-208

Human hazard profile

1. **Does the nanomaterial fulfil the HARN paradigm?**

   Answer: No
   Argument and explanation: The primary C60 molecule has the shape of a soccer ball and has a diameter of less than 1 nm. At concentrations above the solubilisation limit C60 spontaneously form aggregates or so-called fullerene crystals of 25-500 nm in various suspension including water, ethanol and acetone (Shinohara *et al.* 2009)

2. **Is the bulk form of the nanomaterial known to cause or may cause serious damaging effects, i.e. is the bulk form classified according to the CLP with regard to one or more serious health hazards such as germ cell mutagenicity, carcinogenicity or reproductive toxicity in category 1A, 1B or 2?**

   Answer: Not relevant
   Argument and explanation: No bulk form of C60 exists

3. **Is the bulk form of the nanomaterial classified for other less severe adverse effects according to the CLP such as skin corrosion/irritation category 2 and specific target organ toxicity-single exposure category 3?**

   Answer: Not relevant
   Argument and explanation: No bulk form of C60 exists

4. **Is the specific nanomaterial known to be acute toxic?**

   Answer: No
   Argument and explanation: According to Stone *et al.* (2009):
   "…different fullerene types have been shown in two studies to have a very low toxicity after oral exposure as no signs of toxicity have been described for the doses tested. From the identified data it might be possible to derive a NOAEL of 2000 mg kg-1 bw for fullerite (mixture of C60 and C70) (Mori et al. 2006) and of 50 mg kg-1 for polyalkylsufonated (water soluble) C60 (Chen et al. 1998b). As only one dose was tested and no dose with an effect has been determined (reported) it might be possible that a higher NOAEL could be determined, especially for the polyalkylsulfonated C60."…

   "*Following pulmonary exposure fullerenes have shown no or low ability to induce inflammation or even anti-inflammatory responses.*"…

   "*The only identified study investigating effects following dermal exposure (human patch test with fullerene soot) found no detrimental outcome.*"

   "*Following intraperitoneal injection kidney, liver and spleen have been demonstrated to be a target of fullerene toxicity. An LD_{50} of 600 mg kg-1 was determined. Mice have shown to be able to generate antibodies against the C60 derivatives, which were also active against other nanoparticles (SWCNT). The relevance of the findings following intraperitoneal injection for primary routes of exposure (inhalation, dermal and oral) has to be further examined in light of the questionable uptake via these routes.*" (Stone *et al.* 2009).

5. Are there indications that the nanomaterial causes genotoxic, mutagenic, carcinogenic, respiratory, cardiovascular neurotoxic or reproductive effects in humans and/or laboratory animals or has organ-specific accumulation been documented?

   Answer: Maybe
   Argument and explanation:

a. Genotoxicity and mutagenicity: A number of genotoxicity test have been reported on in the scientific literature. For a recent review, see Stone *et al.* (2009). Studies on C60 suspended in solvents were considered irrelevant for C60 LuBExtreme and so was studies reported on fullerol. A couple of studies has found evidence of genotoxicity of C60. Dhawan *et al.* (2006) investigated whether C60 was able to inflict DNA damage within human lymphocytes, and was detected using the Comet assay, when exposed at concentrations ranging from 0.42 to 2100 μg l-1, for up to 6 hours. Sera *et al.* (1996) investigated the mutagenic effect of fullerene exposure (up to 30 μg per plate, for 48 hours) on Salmonella typhimurium, in light and dark conditions using the Ames test. If exposure occurred within the dark, no mutagenic responses were evident. In contrast, a mutagenic effect was observed, when exposure occurred in the presence of visible light, due to the production of ROS, which interact with DNA to elicit damage, and was typified by the formation of 8-hydroxydeoxyguanosine. Lipid peroxidation was also increased by fullerene exposure in light, further highlighting the oxidative consequences associated with light irradiation. Stone *et al.* (2009) concludes: "Genotoxicity has not been associated with fullerene exposure in a number of studies. Mori *et al.* (2006) investigated the mutagenicity of a C60/C70 mixture. It was illustrated that no mutagenic responses were evident within a variety of Salmonella typhimurium and Escherichia Coli strains, using the Ames test (up to 5000 μg per plate). In addition, within the chromosomal aberration test (in CHL/IU hamster lung cells) no aberrations within the structure or number of chromosomes were apparent. Furthermore, Jacobsen *et al.* (2008) investigated the mutagenicity associated with a number of carbon based nanoparticles, including C60 within the mouse FE1-Muta epithelial cell line. It was demonstrated that C60 exposure (0-200 μg ml-1, 24 or 576 hours) was associated with a slight increase in ROS production in cells and in cell free conditions, but no impact on cell viability was observed. C60 was not capable of eliciting strand breaks, and no alterations in mutation frequency were observed when using the Comet assay." Thus, according to Stone *et al.* (2009) the evidence of genotoxicity of C60 is contradictory and therefore difficult to interpret from the studies conducted so far.

b. Respiratory tract toxicity: Following pulmonary exposure fullerenes have shown no or low ability to induce inflammation or even anti-inflammatory responses according to Nielsen *et al.* 2008 and Stone *et al.* (2009). Sayes *et al.* (2007a), however, did observe an increase in the percentages/numbers of Bronchoalveolar lavage (BAL)-recovered neutrophils (i.e. white blood cells) after intratracheally instillation of C60 and hydroxylated C60 i.e. C60(OH)24 just 1 day post-exposure. Sayes *et al.* (2007a) also observed a significant increase in lipid peroxidation values and an increase in level of glutathione (GSH), after 1 week. Lai *et al.* (2000) also observed a significant increase in lipid peroxidation products after intravenous administration of 1 mg C60(OH)18 per kg into male mongrel dogs previously induced with infusion/reperfusion injury. In contrast to Sayes *et al.* (2007a), Lai *et al.* (2000) observed a decrease in the GSH level in intestinal tissue. Adelman *et al.* (1994) observed a reduction of the viability of bovine alveolar macrophages compared to control after exposure to sonicated C60 along with increased levels of cytokine mediators of inflammation (i.e. TNF, IL-6 and IL-8) whereas Baierl *et al.* (1996) and Porter *et al.* (2006) found that C60 and raw soot was not toxic towards bovine- and human alveolar macrophages. The alveolar macrophage serves as the first line of cellular defense against respiratory pathogens (Rubins 2003) and hence studies reporting on the effects on alveolar macrophages are of special interests.

c. Cardiovascular toxicity: To the best of our knowledge no epidemiological or animal study has been reported on in the scientific literature investigated the effects of C60 on the cardio-vascular system.

d. Neurotoxicity: To the best of our knowledge no epidemiological or animal study has been reported on in the scientific literature investigated the neutotoxic potential of C60.

e. Reproductive damage: Stone *et al.* (2009) recently reviewed the reproductive toxicology of fullerenes. Three studies were reviewed, however only one of them are considered directly relevant for C60 LuBExtreme. In one study C60 had been solubilised in polyvinylpyrrolidone and administered intraperitoneally to pregnant mice (Tsuchiya *et al.* 1996) and in another THF suspended C60 was used to study the cytotoxicity of C60 in Chinese hamster ovary mammalian cell line (Han and Karim 2009). PVP and THF is not used in the production of C60 LuBExtreme and hence these studies were found to be only partially relevant. Collectively, these results, illustrate the potential toxicity of fullerene particles in mammalian ovary cells (Stone *et al.* 2009). However studies are extremely limited in number and in sample size. Only one study identified examined effects on an

ovarian cell line model with no studies focused on other organs or cell types in the female reproductive system. No specific in vitro or in vivo studies were found examining fullerene effects in male reproductive system.

f. Carcinogenicity: To the best of our knowledge no epidemiological or animal study has been reported on in the scientific literature investigated the carcinogenic potential of C60.

g. Does the nanomaterials accumulate in tissue and/or organs?: According to Stone *et al.* (2009) *"Information regarding the ADME profile of fullerenes is generally lacking, and therefore warrants further investigation in future studies. In the small number of studies described here, it would appear that the majority of fullerenes remain at the deposition site (specifically within the lungs and gut), but that it is also possible for fullerenes to cross cell barriers and to be transported within the blood. Accumulation appears to be predominant within the liver, kidneys and spleen, with evidence of toxicity also manifesting at sites of accumulation. Metabolism of fullerenes has also been suggested, and the consequences of this require consideration. Elimination of fullerenes within the faeces and urine has also been demonstrated, which may reduce their propensity for distribution and toxicity. However, it is relevant to note that the representative nature of the limited number of findings, for all fullerene derivatives is unknown at this time."*

Stone *et al.* (2009) furthermore state that: *"The findings from the different studies therefore share the commonality, that subsequent to injection, fullerenes preferentially accumulate within the liver. Therefore it is of high relevance to evaluate the impact of fullerene accumulation on liver function, and to assess the contribution of the liver to the metabolism of fullerenes and, in addition to considering the ability of the liver to facilitate the removal of fullerenes from the body within bile, and therefore the faeces."*

The overall answer to this question is "Maybe" based on the following considerations:

1. Mutagenic effect have been observed, when exposure occurred in the presence of visible light, due to the production of ROS, which interact with DNA to elicit damage whereas the evidence of genotoxicity of C60 is contradictory and therefore difficult to interpret from the studies conducted so far.

2. In regard to respiratory damage an increase in the percentages/numbers of Bronchoalveolar lavage (BAL)-recovered neutrophils (i.e. white blood cells) after intratracheally instillation has been reported and so has a reduction of the viability of bovine alveolar macrophages

3. Based on studies found only to be partially relevant for C60 LubExtreme data of reproductive damage collectively illustrate the potential toxicity of fullerene particles in mammalian ovary cells.

4. To the best of our knowledge no epidemiological or animal study has been reported on in the scientific literature investigated the carcinogenic-, cardio-vascular and neurotoxic potential of C60.

5. Though indications of accumulation of fullerenes in organs have been described the very few findings that exist at this point in time rather call for the answer "maybe" than the answer "yes"

6. Overall evaluation of human hazard

Based on a holistic evaluation of the evidence summarized above and sub-conclusion reached, we concluded that the color-code that best reflects the human hazard profile of C60 in C60 LuBExtreme is • based on in vitro evidence indicating at least one nanospecific hazard.

Environment hazard profile

1. **Bulk material classified as CLP Acute 1 or Chonic 1 or Chronic 2?**

   Answer: No
   Arguments and explanation: C60 does not have a meaningful bulk parent materials and hence the answer to this question is no by default.

2. **Is the nanomaterial in question reported to be hazardous to environmental species i.e. LC_{50} or EC_{50} <10 mg/l?**

   Answer: Yes
   Arguments and explanation: According to Stone *et al.* (2009) "*The information available so far leads to the conclusion that non-functionalised C_{60} is toxic for aquatic organisms. A study with fish observed sub-lethal effects on growth at 0.04 mg l^{-1}*".
   In the short-term studies with crustaceans lethal concentrations were 7.9 mg l^{-1} (LC_{50}) for D. magna exposed to sonicated C60 and over 22.5 mg l^{-1} for copepod species exposed to stirred C60. Long-term exposure of Daphnia magna to 2.5 mg l^{-1} C60 revealed in a delay of moulting and a significant reduction in offspring. However, the effect on reproduction could have been caused by mortality which occurred from day 5 onwards. A $NOEC_{Daphnia}$ (long-term) should be < 2.5 mg l^{-1} C60 (Stone *et al.* 2009). Hence non-functionalized C60 has been reported to be hazardous to environmental species i.e. LC_{50} or EC_{50} <10 mg/l and this indicator is fulfilled which leads to the color code of "red"

3. Overall evaluation of environmental hazard

We concluded that the color-code that best reflects the environmental hazard profile of C60 used in C60 LuBExtreme is • **based on nanospecific LC_{50} or EC_{50} < 10 mg/l.**

Summary

This information provided and summarized in this template is considered to be accurate at the date of printing and is believed to be a complete reflection of what the Ex-Lub knows about the risks of using C60 as an additive to enhance the performance of C60 LuBExtreme.

Exposure			Effects	
Prof	**Consum**	**Environ**	**Human**	**Environ**
●	●	●	●	●
			7b[a)]	2[b)]

Red, yellow and green indicate high, medium and low indication of exposure/effect level whereas grey indicates too limited data to assess exposure/effect; a) "based on in vivo evidence of a combination of hazards from testing of the nanomaterial" (see Appendix 2, Table A2.1); b) "based on LC_{50} or EC_{50} < 10 mg/l for the testing of the nanomaterial" (see Appendix 2, Table A2.2)

The overall **NanoRiskCat** code for the C60 in C60 LubExtreme is ●●●|●●

NanoRiskCat does not lead directly to a decision, but provides a basis for decision-making by defining a number of concrete criteria that defines to which extend there are indication of exposures and effects for professional users, consumers, and the environment.

It is the reader's obligation to evaluate this NRC in the light of any new scientific evidence regarding risks published after the data of printing and to comply with all applicable laws and regulations.

Date of printing **Signature**

……/……/…… ……..

4.2 Case study 2: TiO_2 in sunscreen

The following case study is an example of how one could use NanoRiskCat on TiO_2 used in sunscreen. The case is based on a realistic use of TiO_2 in a product available for professional and non-professional users. While real data from litterature is used, the product name is constructed. NanoRiskCat is applied to this product filling out the information being asked for in the NRC template available in appendix 1 by using the guidance provided in Chapter 3 as well as the series of tables available in Appendix 1 and the additional sentences for explaining color codes in Appendix 2.

NanoRiskCat

Subject: TiO_2 **in SunPro SPF 50 by SunProMax**

Nanomaterial description	
Material source or producer:	TiO_2 Ltd (SunProMax is not primary producer of TiO_2)
Manufacturing process:	Flame hydrolysis
Appearance:	White powder
Chemical composition:	TiO_2, uncoated
Physical form/shape:	Powder/spherical
Purity:	> 95% rutile
Size distribution:	20-25 nm
Solubility:	Insoluble (H_2O)
State of aggregation or agglomeration:	70-90 nm aggregates/agglomerates
CAS number (if applicable):	1317-80-2

Product description

SunPro SPF entails 15% 20-25 nm nanoTiO_2. NanoTiO_2 is used as a sunfilter that protects against UVB as well as UVA. SunPro SPF 50 reduction of UVA and UVB is 90% and 96%, respectively. SunPro SPF 50 does not penetrate the skin, but acts as a protecting white layer on the skin that reflects the sunrays. This type of filters is called physical filters and is well suited for the both kids and adults.

Applications

It is important to use plenty of sunscreen, 30-40 ml, in order to achieve the optimal effect. In order to achieve the optimal protection the sunscreen should be applied before sunbathing is initiated and repeated depending on the need. Never let infants stay directly exposed to the sun. Always protect children against intense sunrays by making them wear hat and appropriate clothes. Furthermore, avoid exposure to the sun in the middle of the day, i.e. 12-15 pm, when the sunrays are the most intensive.

Exposure potential for professional end-users

According to table 4 in chapter 3 of the **NanoRiskCat** main report on Criteria for evaluating the exposure profile, the following REACH Use Descriptor Categories are relevant for SunPro SPF 50.

REACH Cat.	#	Description	**Examples and explanations**
PROC	Not applicable		
PC	39	Cosmetics, personal care products	

FC	Not applicable		

Exposures to the professional end-users of SunPro SPF50 are multiple and to be expected. As full body skin exposure is recommended when exposed to sunrays, and although minor levels of ingestion is to be expected, inhalation can be ruled out.

No PROC or FC was found to be relevant for the use of TiO_2 in SunPro SPF50.

Considering the color-codes of PC34 (●), we concluded that the overall

Exposure potential for professional end-users is ●

Consumer exposure potential

According to table 4 in chapter 3 of the **NanoRiskCat** main report on Criteria for evaluating the exposure profile, the following REACH Use Descriptor Categories are relevant for SunPro SPF 50.

REACH Cat.	#	Description	**Examples and explanations**
PC	39	Cosmetics, personal care products	
AC, no intented release	Not applicable		
AC, intented release	Not applicable	<<Insert description of this AC, intended release >>	

Consumer exposure to SunPro SPF 50 are multiple and to be expected. As full body skin exposure is recommended when exposed to sunrays, and although minor levels of ingestion is to be expected, inhalation can be ruled out.

No AC, no intended release or AC, intended release was found to be relevant for the use of TiO_2 in SunPro SPF50.

Considering the color-codes of the PC39 (●), we concluded that the overall

Consumer exposure potential is ●

Environmental exposure potential

According to table 4 in chapter 3 of the **NanoRiskCat** main report on Criteria for evaluating the exposure profile, the following REACH Use Descriptor Categories are relevant for SunPro SPF 50.

REACH Cat.	#	Description	**Examples and explanations**
AC, no intended release	<<Insert number of first relevant AC, no intended release >>	<<Insert description for this AC, no intended release >>	<<Insert examples and explanations for this AC, no intended release >>
AC, intended release	Not applicable		
ERC	8a	Wide dispersive indoor use of processing aids in open systems	Indoor use of processing aids by the public at large or professional use. Use (usually) results in direct release into the environment/sewage system, for example, detergents in fabric washing, machine wash liquids and lavatory cleaners, automo-

			tive and bicycle care products (polishes, lubricants, deicers), solvents in paints and adhesives or fragrances and aerosol propellants in air fresheners.
ERC	8d	Wide dispersive outdoor use of processing aids in open systems	Outdoor use of processing aids by the public at large or professional use. Use (usually) results in direct release into the environment, for example, automotive and bicycle care products (polishes, lubricants, deicers, detergents), solvents in paints and adhesives.

Environmental exposure to SunPro SPF 50 are multiple and to be expected.

The main outlets to the environment are expected to be directly into the water recipients and/or indirectly via the STPs into water recipient and soil.

Considering the color-codes of the ERC 8a(•) and ERC 8d(•), we concluded that the overall

Environmental exposure potential is ●

Literature methodology/sources of information

Two sources of information were used to fill out the NanoRiskCat for TiO_2:

1. Stone V, Hankin S, Aitken R, Aschberger K, Baun A, Christensen F, Fernandes T, Hansen SF, Hartmann NB, Hutchinson G, Johnston H, Micheletti G, Peters S, Ross B, Sokull-Kluettgen B, Stark D, Tran L. 2009. Engineered Nanoparticles: Review of Health and Environmental Safety (ENRHES). Available at: http://nmi.jrc.ec.europa.eu/project/ENRHES.htm (Accessed July 15, 2010)
2. Shinohara, N., Nakamishi, J., Gamo, M. 2009. Risk Assessment of Manufactured Nanomaterials – TiO_2. (Available: http://www.aist-riss.jp/main/modules/product/nano_rad.html?ml_lang=en (Accessed July 15, 2010)

Human hazard profile

1. **Does the nanomaterial fulfil the HARN paradigm?**

   Answer: No
   Arguments and explanation: Nanoparticles used in SunPro SPF 50 by SunProMax are 20-25 nanometer and spherical

2. **Is the bulk form of the nanomaterial known to cause or may cause serious damaging effects, i.e. is the bulk form classified according to the CLP with regard to one or more serious health hazards such as germ cell mutagenicity, carcinogenicity or reproductive toxicity in category 1A, 1B or 2?**

   Answer: No
   Arguments and explanation: To the best of our knowledge TiO_2 has no CLP classifications

3. **Is the bulk form of the nanomaterial classified for other less severe adverse effects according to the CLP such as skin corrosion/irritation category 2 and specific target organ toxicity-single exposure category 3?**

   Answer: No
   Arguments and explanation: To the best of our knowledge TiO_2 has no CLP classifications

4. **Is the specific nanomaterial nanoform of the materials known to be acute toxic?**

Answer: No
Arguments and explanation: According to Stone *et al.* (2009) no in vivo studies have been identified in regard oral and dermal acute toxicity. In regard to inhalation toxicity, several authors have shown that TiO_2 nanoparticles (with a size in the range of about 20-30 nm) is considerably more toxic than its micro- TiO_2 (> 100nm) counterpart (see e.g. Ferin *et al.* 1992; Renwick *et al.* 2004; Chen *et al.* 2006; Inooue *et al.* 2008). After having exposed 2 times 10 mice to nanoTiO_2 via intraperitional injection, Chen *et al.* (2006) reported observing that a total of five mice died after exposure to 1944 and 2592 mg/kg, respectively. From this can be derived that the acute toxicity estimates are > 5 mg/l.

5. Are there indications that the nanomaterial causes genotoxic, mutagenic, carcinogenic, respiratory, cardiovascular neurotoxic or reproductive effects in humans and/or laboratory animals or has organ-specific accumulation been documented?

Answer: Yes
Arguments and explanation:

a. Genotoxicity and mutagenicity: According to Stone *et al.* (2009) "TiO_2 *nanoparticles are not expected to cause direct mutagenicity/genotoxicity (although further testing may be needed to fully confirm this), but may trigger genotoxicity via an indirect threshold driven mechanism involving oxidative stress.*"

b. Respiratory tract toxicity: According to Stone *et al.* (2009) several authors have shown that TiO_2 nanoparticles (with a size in the range of about 20-30 nm) is considerably more toxic than its micro- TiO_2 (> 100nm) counterpart (see e.g. Ferin *et al.* 1992; Renwick *et al.* 2004; Chen *et al.* 2006; Inooue *et al.* 2008). Most studies identified used a single dose of particles, administered via intratracheal instillation and toxicity observed included: pulmonary inflammatory response (characterised by neutrophil and macrophage infiltration) (Ferin *et al.* 1992; Chen *et al.* 2006; Warheit *et al.* 2007; Inoue *et al.* 2008; Renwick *et al.* 2004; Grassian *et al.* 2007); epithelial damage, increased permeability of the lung epithelium, and cytotoxicity, which were measured within the bronchoalveolar lavage fluid (BALF) (Renwick *et al.* 2004); and morphological alteration within the lung (Chen *et al.* 2006). Finally, Ahn *et al.* (2005) using a high dose (4 mg kg^{-1}) investigated what processes were responsible for particulate mediated stimulation of excessive mucus secretion within humans. TiO_2 exposure stimulated an increase in goblet cell hyperplasia, which is, in part, attributed to an increase in muc5 gene expression and IL-13 production. Therefore, it could be speculated that particle mediated increases in mucus secretion contributed to the aggravation of chronic airway disease symptoms within humans, and therefore warrants further investigation. Grassian *et al.* (2007) investigated the toxicity of TiO_2 nanoparticles (5 and 21 nm) within mice, subsequent to inhalation (0.7 or 7 mg m^{-3}, for 4 hours) or nasal instillation (up to 150 µg per 50 µl). An elevated macrophage population was associated with the inhalation of particles (4 and 24 hours post exposure), and were observed to internalise particles. An infiltration of neutrophils was associated with the nasal instillation of TiO_2. Several authors suggested that the response subsequent to TiO_2 exposure was dose driven (e.g. Chen *et al.* 2006; Renwick *et al.* 2004). In the Renwick *et al.* (2004) study, no toxicity was seen at 125 µg per rat (corresponding to 0.5 µg kg^{-1} assuming a rat weight of 250 g), whereas toxicity was seen at the high dose of 500 µg per rat (particle size 29nm). Chen *et al.* (2006) exposed mice and found toxicity (inflammation and histological changes in the lung) at the lowest dose of 100 µg per mouse (corresponding to 33 µg kg^{-1} assuming a mouse weight of 30 g) (particle size 19-21 nm). Although the Chen *et al.* (2006) study does not indicate a no effect level, it seems justified (assuming the rat is more sensitive) to estimate, a No Observed Adverse Effect Level (NOAEL) of 125 µg per rat (corresponding to 0.5 µg kg^{-1}). The crystallinity of TiO_2 nanoparticles is thought to influence the toxicity with the anatase form expected to be more toxic that the rutile form (Warheit *et al.* 2007).

c. Cardio-vascular toxicity: According to Stone *et al.* (2009) "*Helfenstein et al. (2008) showed that* TiO_2 *nanoparticles were able to affect cardiomyocyte electrophysiology, enhance ROS production, and reduce myofibril organisation, whereas Peters et al. (2004) found* TiO_2 *relatively low-toxic to HDMEC endothelial microvascular cells (with minimal IL-8 release).*"

d. Neurotoxicity: Long *et al.* (2006, 2007) indicates that TiO_2 nanoparticles caused a ROS driven toxicity to some types of cells of the CNS in vitro. According to Stone *et al.* (2009) *"Wang et al. (2008a) investigated the distribution of rutile (80 nm) and anatase (155 nm) TiO_2 particles within the mouse brain, following nasal instillation exposure (500 µg per mouse, every other day for a total of 30 days) and determined if any neurotoxicity associated with exposure. Both forms of TiO_2 were able to access the brain, with accumulation within the cerebral cortex, thalamus and hippocampus evident, and was postulated to occur via the olfactory bulb. This route of uptake however, was unlikely to be mediated via penetration into the cardiovascular system and via the blood. Instead, TiO_2 delivery to the brain occurred via neuronal transport, with preferential localisation evident within the hippocampus and olfactory bulb. Accumulation of TiO_2 resulted in morphological alterations and loss of neurones in the hippocampus, which was accounted for by the higher distribution of TiO_2 within this brain region. In addition it was suggested that TiO_2 elicited oxidative stress within the brain due to the elevation of superoxide dismutase (SOD), and catalase activity, and evidence of increased lipid peroxidation and protein oxidation. Therefore neuronal mediated translocation of TiO_2 to the brain, following nasal instillation, was observed, with the hippocampus illustrated as being the main target of accumulation and toxicity. Wang et al. (2008b) expanded upon these findings and found that the phenomenon was time dependent (was maximal at 30 days), and that an inflammatory response (indicated by IL-1β, and TNFα) within the brain was also stimulated by TiO_2 exposure. The response was measured at day 2, 10, 20, and 30. It was apparent that repeated exposures, over a period of 30 days, were required to enable the accumulation of TiO_2 within the brain. It is therefore of interest that the neuronal transport of nanoparticle containing substances between the nose and CNS could be exploited, in order to bypass the blood brain barrier".*

e. Reproductive damage: Komatsu *et al.* (2008) has shown that TiO_2 nanoparticles are taken up by and affect viability, proliferation and gene expression of Leydig cells (testosterone producing cells of the testis) in vitro, whereas one in vitro study suggests that TiO_2 nanoparticles may be toxic towards Leydig cells. However, given the toxico-kinetics, it can be questioned whether TiO_2 can indeed reach these cells. No studies investigating female fertility were identified. Overall, no conclusion can be drawn (Stone *et al.* 2009). No information has been identified on developmental toxicity and hence and no conclusion can be drawn.

f. Carcinogenicity: One study has described finding tumour following chronic inhalation after repeated exposure (Heinrich *et al.* 1995). The study used very high doses and had a long duration (high death in the control group). NIOSH (2005) concluded, based on those data that TiO_2 is carcinogenic in rats and that it cannot be excluded to be carcinogenic in humans. It is expected that carcinogenicity occurs following pulmonary overload and thus has a threshold (Stone *et al.* 2009). It should be noted that also the International Agency for Research on Cancer have assessed TiO_2 (even the microform – if exposure is high enough) to be a Class 2B carcinogen (Possibly carcinogenic to humans) (IARC 2006).

g. Does the nanomaterials accumulate in tissue and/or organs?: As noted by Stone *et al.* (2009) there is limited evidence in regard to whether TiO_2 accumulate in tissue and/or organs. According to Stone *et al.* (2009) *"Fabian et al. (2008) determined the tissue distribution of TiO_2 nanoparticles (20-30 nm) within rats, at 1, 14 and 28 days post exposure, via intravenous injection (5 mg kg-1). TiO_2 was cleared from the blood and primarily accumulated within the liver, but was also apparent within the spleen, lungs and kidneys. The level of TiO_2 was retained over the observation time within the liver, however levels decreased with time within the other organs. No serum cytokine or enzyme changes, which insinuated that no toxicity was associated with TiO_2 exposure, however further investigations, including histopathological analysis would be necessary to confirm this. Wang et al. (2008a) investigated the distribution of rutile (80 nm) and anatase (155 nm) TiO_2 particles within the mouse brain, following nasal instillation exposure (500 µg per mouse, every other day for a total of 30 days) and determined if any neurotoxicity associated with exposure. Both forms of TiO_2 were able to access the brain, with accumulation within the cerebral cortex, thalamus and hippocampus evident, and was postulated to occur via the olfactory bulb."*

6. Overall evaluation of human hazard

The overall answer to this question is "Yes" based on the following considerations:

1. The widely reported respiratory damage caused by nanoTiO_2

2. NanoTiO_2 has been associated with carcinogenic-, cardiovascular and neurotoxic and reproductive damage

We conclude that the color-code that best reflects the human hazard profile of TiO_2 used in SunPro SPF50 is ● based on in vivo evidence indicating at least one nanospecific hazard

Environment hazard profile

1. **Bulk material classified as CLP Acute 1 or Chronic 1 or Chronic 2?**

   Answer: No
   Arguments and explanation: Bulk TiO_2 has to the best of our knowledge not be classified a CLP Acute 1 or Chronic 1 or 2

2. **Is the nanomaterial in question reported to be hazardous to environmental species i.e. LC_{50} or EC_{50} <10 mg/l?**
   Answer: Yes
   Arguments and explanation: Following U.S. Environmental Protection Agency (2002) standard protocol, Zhu *et al.* (2008) reported deriving an $LC_{50,72h}$ of 2.02 mgl-1 for nano- TiO_2 on the crustacean Daphnia magna.

3. **Overall evaluation of environmental hazard**

   The overall answer to this question is "Yes" based on the fact that nano- TiO_2 has been reported to be hazardous to environmental species i.e. LC_{50} or EC_{50} <100 mg/l and this indicator is fulfilled which leads to the color code of "red"

We concluded that the color-code that best reflects the environmental hazard profile of TiO_2 used in SunPro SPF50 is ● based on nanospecific LC_{50} or EC_{50} < 10 mg/l

Summary

This information provided and summarized in this template is considered to be accurate at the date of printing and is believed to be a complete reflection of what the SunProMax knows about the risks of using TiO_2 as an UV filter to reflect UVA and UVB sunrays in SunPro SPF50.

Exposure			Effects	
Prof	**Consum**	**Environ**	**Human**	**Environ**
●	●	●	●	●
			8b[a)]	2[b)]

Red, yellow and green indicate high, medium and low indication of exposure/effect level whereas grey indicates too limited data to assess exposure/effect; a) "based on in vitro evidence of a combination of hazards from testing of the nanomaterial" (see Appendix 2, Table A2.1); b) "based on LC_{50} or EC_{50} < 10 mg/l for the testing of the nanomaterial" (see Appendix 2, Table A2.2)

The overall **NanoRiskCat** code for the use of TiO_2 in SunPro SPF50 is: ●●●|●●

NanoRiskCat does not lead directly to a decision, but provides a basis for decision-making by defining a number of concrete criteria that defines to which extend there are indication of exposures and effects for professional users, consumers, and the environment

It is the reader's obligation to evaluate this NRC in the light of any new scientific evidence regarding risks published after the data of printing and to comply with all applicable laws and regulations.

Date of printing **Signature**

……/……/…… **……..**

5. Use(s) of NanoRiskCat

In previous chapters of this report the structure of the decision-support tool NanoRiskCat has been described. The development of NanoRiskCat was initiated after a need had been identified for the development of a new concept to provide support to companies and regulators in regard to identifying, ranking and communicating their knowledge of the risks of nanomaterials in specific uses in products.

5.1 Communication of the results of NanoRiskCat

In its simplest form the final outcome of using NanoRiskCat for a nanomaterial in a given application will be communicated in the form of a short title describing the use of the nanomaterial and five color-coded dots (e.g. •••| ••). The red, yellow and green colored dots respectively indicate high, medium and low indication of exposure or effect whereas the grey indicates that the data available is too limited to assess the possibility for exposure or effect. It's important to underline that the color refers to a high/medium/low ***indication*** of exposure/hazard and does not in itself give a ***definitive*** categorization.

NanoRiskCat is focussed on evaluating the nanomaterial as an ingredient under the physical conditions it occurs under in the product. Hence, NanoRiskCat does not evaluate exposure and effects from the other constituents and impurities in the product nor does it take into account the specific content of nanomaterial in the product. Thus, NanoRiskCat is directed towards the generic use descriptors and scenarios, which for instance are apparent in the product categories used in REACH. It is the hope the NanoRiskCat will contribute to the safe handling nanomaterials in specific applications and it is important to underline that filling out NanoRiskCat cannot be used to pass judgment about the safety of other applications of a given nanomaterial.

NanoRiskCat can primarily be used to understand and categorize what is known about the hazard and exposure of using a given nanomaterial in a given application. By following the sketched format provided in NanoRiskCat and by filling out the NRC template provided in Appendix 1, users will be able to sort, systematize and structure human and environmental hazard information on nanomaterials into an easily understandable and communicable format. The final outcome of NanoRiskCat (the short title of use scenario, the color coding and standard sentences) will make it clear whether it is the professional end-users, consumers and/or the environment that is primarily exposed and whether there are high, medium and low indications of human and environmental effects. NanoRiskCat may also inform users of what kind of information is currently not available. For instance, it might be an element of concern if there is a high indication of environmental exposure, but not data available on the environmental hazards of the nanomaterial.

5.2 Pros and cons of NanoRiskCat

The NanoRiskCat code of C_{60} in lubricant was •••|•• based on ***in vitro*** evidence indicating at least one nanospecific human hazard and nanomaterial

specific LC_{50} or EC_{50} values below 10 mg/l indicating environmental hazard. For TiO_2 in sunscreen the NanoRiskCat code was ●●●|●● based on ***in vivo*** evidence indicating at least one nanospecific human hazard being associated with nanoTiO2 and a nanomaterial specific LC_{50} or EC_{50} < 10 mg/l for daphnids indicating environmental hazard.

When interpreting these color codes, it is important to be aware of the strengths and weaknesses of NanoRiskCat. A significant strength of NanoRiskCat is that it can be used even in cases where lack of data is prominent and hampers the completion of traditional risk assessment procedures. Another is that the results of NanoRiskCat can be easily communicated with other interested parties. A significant weakness of NanoRiskCat is that many of the cut-off values used primarily in the environmental hazard evaluation are based on dose by mass and the assumption that the "dose-makes-the-poison" (i.e. the weight-based dose) which we know is probably not valid for all nanomaterials (Stone ***et al.*** 2009). It is an ongoing discussion on which dose-metrics will be the best to use in nano(eco)toxicology. Furthermore, the process by which the color code is assigned to human hazards associated with the nanoform of a given material is based primarily on scientific expert judgement and a holistic assessment of the evidence of mutagenicity, carcinogenicity, respiratory toxicity, etc. As expert interpretation of the scientific literature can vary so can the conclusion reached and the human hazard color code assigned to nanomaterial. It is not possible to provide clear-cut guidance and rules at this point in time for how to complete a holistic evaluation of the human and environmental hazards associated with the nanoform of a given material. Although some might argue that this is something to strive and wish for, it could be argued that rigid rules would put a significant straitjacket on the emerging and exploratory field of nano(eco)toxicology and our ability to make decisions based on the newest available science.

Besides being helpful for users to sort out information and structure and communicate their knowledge, NanoRiskCat can furthermore be used to do a comparative analysis of two or more nanomaterials for the same application. Assuming, for instance, that the exposure profiles are the same for the two materials (i.e. ●●●), a comparative analysis of one or more alternatives would be narrowed down to an interpretation of the hazard profile of the two materials. To make a final conclusion about one being "more safe" than the other it is, however, necessary to take account of the respective concentrations of the nanomaterial in the products, the hazardous properties and the concentration of the other constituents in the products and whether there are any differences in the handling and the exposure potential between the products. Also it is important to evaluate if the identified hazards are associated to a specific exposure route and whether this exposure route is relevant for the product and its use i.e. whether a red spot for exposure match to a red spot for the hazard (same exposure route). Thus as a screening tool, NanoRiskCat gives an indication that has to be further verified before a final decision can be made.

5.3. Stakeholder-dependent uses of NanoRiskCat

Decisions that could come out of using NanoRiskCat are stakeholder-dependent. The tool in itself does not lead directly to a decision, but provides a more informed basis for decision-making by including a number of indica-

tors that define whether exposure and effects are likely (or unlikely) to occur and whether the nanomaterial may have harmful properties of concern.

Companies can use NanoRiskCat to communicate their knowledge about the exposure and effects of the nanomaterial they use by filling out the NanoRiskCat template and by making it available to interested parties. They could assess the need to develop guidance for safe uses that e.g. limit exposures and/or work systematically with designing safer applications of nanomaterials. Companies/designers could furthermore use NanoRiskCat to choose safer alternatives/applications of nanomaterials in their products.

Besides using NanoRiskCat as a screening tool to flag nanomaterial use of concern and hence subject for further investigation, regulators could use NanoRiskCat to set default guidance for when regulatory measures are to be implemented e.g. the need to consider implementation of precautionary measures that could be triggered by default if the color code of a given nanomaterial application is all red or if there are – say for instance -indications of high levels of environmental exposure and environmental hazards. Regulators could also decide to develop guidance on controlled uses. For instance, requirements could be made for the use of specific personal protection equipment if there is a high level of exposure to professional end-users. Finally, regulators could use NanoRiskCat to set research prioritizes for instance if there is an indication of high level of exposure, but a lot of "maybes" or unknowns in regard to human and environmental hazards.

Down-stream users (e.g. consumers) can use NanoRiskCat to make a preliminary assessment of a range of nanomaterials as a means to select the seemingly most benign material. Furthermore, independent parties such as academics and non-governmental organizations can use the tools to learn more about what companies know about exposure and effect of their nanomaterials and they can use NanoRiskCat to do their own evaluation and engage in an informed dialogue about nanorisks.

It is important to emphasize that it has not been possible within the framework of this project to make a further validation of the NRC concept. To promote a wider use of the tool it is considered necessary to perform additional case studies and if relevant adjust the processes and decision criteria in order to obtain a screening tool as informative and practical as possible.

6. Conclusion

This project was aimed at developing a conceptual framework for assisting manufacturers, down-stream end users, regulators and other stakeholders to evaluate, rank and communicate exposure and effect levels associated with the specific applications of a given nanomaterial. This is done through the framework NanoRiskCat by providing a detailed, qualitative, tiered approach for screening of indications of exposure and effects of nanomaterials. In NanoRiskCat exposure and effects are evaluated in the following sequence:

1. Exposure potential for professional end-users
2. Exposure potential for consumers
3. Exposure potential for the environment
4. A preliminary hazard evaluation for humans and
5. A preliminary hazard evaluation for the environment

A generic template for mapping and reporting these five aspects for a specific application of a given nanomaterial has been developed and can be found in Appendix 1 of this report.

In its simplest form the final outcome of using NanoRiskCat for a nanomaterial in a given application will be communicated in the form of a short title describing the use of the nanomaterial (e.g. MeO in ship paint) and a color code consisting of five dots (e.g, ●●●|●●) where the first three dots always refer to potential exposure of professional end-users, consumers and the environment in that sequence and the last two colors always refer to the hazard potential for humans and the environment. The colors signify whether the indications of exposures and effects separately are high (red), medium (yellow), low (green), or unknown (grey). To help communicate the scientific reasoning behind assigning a human health and environmental hazard classification and why a given nanomaterial was assigned red, yellow or grey, a number of default statements have been developed. These standard sentences are meant to reflect primarily whether the conclusion has been reached based on ***in vivo*** or ***in vitro*** studies and in regard to what endpoint. Depending to the final classification in regard to human health, the user of NRC has to select one or more of those sentences that best reflect the scientific basis for assigning the color code.

While the two cases included in this report by no means can be claimed to validate the NanoRiskCat, they serve a purpose is to illustrate illustrate the feasibility of NanoRiskCat. Thus, the two nanomaterials (titanium dioxide and C60-fullerenes) in two different applications i.e. C60 used in a lubricant and TiO_2 used in sunscreen were used as “training sets” for the conceptual framework. The NanoRiskCat code of C60 in lubricant was ●●●|●● based on ***in vitro*** evidence indicating at least one nanospecific human hazard and a nanomaterial specific LC_{50} or EC_{50} < 10 mg/l indicating environmental haz-

ard. For TiO_2 in sunscreen the NanoRiskCat code was ●●●|●● based on ***in vivo*** evidence indicating at least one nanospecific human hazard and a nanomaterial specific LC_{50} or EC_{50} < 10 mg/l indicating environmental hazard. It is evident that more cases are needed to show the strengths and weaknesses of NanoRiskCat, but this was beyond the scope of the present project.

The use of NanoRiskCat will in itself not lead directly to a decision, but provides a more informed basis for decision-making by including a number of indicators that defines whether exposures and effects are likely (or unlikely) to occur.

It is important to underline that NanoRiskCat is not a product label and NanoRiskCat is only to be used for evaluating the nanomaterial as an ingredient under the physical conditions it occurs in the product. NanoRiskCat does not evaluate exposure and effects from the other constituents and impurities in the product nor does it take into account the specific content of nanomaterial in the product. Thus, NanoRiskCat is directed towards the generic use descriptors and scenarios, which for instance are apparent in the product categories used in REACH. NanoRiskCat will contribute to safety guidance in relation of specific nanomaterial application and it is important to underline that filling out NanoRiskCat cannot be used to pass judgment about the safety of other (all) applications of a given nanomaterial. A strength of NanoRiskCat is that it can be used even in cases where lack of data is prominent and hampers the completion of traditional risk assessment procedures.

Decisions that could come out of using NanoRiskCat are stakeholder dependant. Regulators could use the tools to set default guidance for when regulatory measures are to be implemented, develop guidance on controlled uses and/or set research prioritizes. Companies can use NanoRiskCat to communicate what they know about the exposures and effects of the nanomaterial they use, assess the need to develop guidance for safe uses that e.g. limit exposures and/or work systematically with designing safer nanomaterials and use of these. Down-stream users (e.g. consumers) can use NanoRiskCat to make a preliminary assessment of a range of nanomaterials as a mean select the seemingly most benign material. Furthermore, independent parties such as academics and non-governmental organizations can use the tools to learn more about what companies known about exposure and effect of their nanomaterials and they can use NanoRiskCat to do their own evaluation and engage in an informed dialogue about nanorisks.

It is finally important to stress that the color coding obtained in NanoRiskCat should not be seen as an absolute categorization. It rather serves as a step in an iterative process in which stakeholders in risk-related issues can reach a common – and guided - understanding of the level of potential exposures and effects of nanomaterials in specific products.

It is important to emphasize that it has not been possible within the framework of this project to make a further validation of the NRC concept. To promote a wider use of the tool it is considered necessary to perform additional case studies and if relevant adjust the processes and decision criteria in order to obtain a screening tool as informative and practical as possible.

7. References

Baun, A., Hansen, S.F. 2008. Environmental challenges for nanomedicine. Nanomedicine 2(5): 605-608
.
Baun, A., Hartmann, N.B, Greiger, K.D., Hansen, S.F. 2009. Setting the Limits for Engineered Nanoparticles in European Surface Waters. Journal of Environmental Monitoring 11, 1774 – 1781.

BSI 2007a. Terminology for Nanofabrication. PAS 135:2007. London: BritishStandards Institution.

BSI 2007b. Terminology for Nanomaterials. PAS 136:2007. London: British Standards Institution.

CCA. 2008. Small Is Different: A Science Perspective On The Regulatory Challenges of the Nanoscale. Ottawa: The Council of Canadian Academies.

Davis, J.M., Wang, A., Sharkin, J.A. ***et al.*** 2009. External Review Draft Nanomaterial Case Studies: Nanoscale Titanium Dioxide in Water Treatment and in Topical Sunscreen. EPA/600/R-09/057. July 2009 National Center for Environmental Assessment Office of Research and Development U.S. Environmental Protection Agency Research Triangle Park, NC

ECHA 2008. Guidance on information requirements and chemical safety assessment Chapter R.7a: Endpoint specific guidance http://guidance.echa.europa.eu/docs/guidance_document/information_requirements_r7a_en.pdf?vers=02_02_10.

ECHA 2010. Guidance on information requirements and chemical safety assessment Chapter R.12 Use descriptor system. Version: 2 March 2010 http://guidance.echa.europa.eu/docs/guidance_document/information_requirements_r12_en.pdf).

EEA. 2001. Late Lessons from Early Warnings: The Precautionary Principle 1896–2000. Copenhagen: European Environmental Agency.

Environmental Defense and DuPont. 2007. Nano Risk Framework. Environmental,Defense and DuPont.

EP & CEU. 2008. REGULATION (EC) No 1272/2008 OF THE EUROPEAN PARLIAMENT AND OF THE COUNCIL of 16 December 2008 on classification, labelling and packaging of substances and mixtures, amending and repealing Directives 67/548/EEC and 1999/45/EC, and amending Regulation (EC) No 1907/2006, Official Journal of the European Union L 353/1-1355

Fisher, L. 2007. Envtl. Defense & DuPont to Jointly Launch Risk Framework. June 21 2007 available at http://www.wilsoncenter.org/ondemand/index.cfm?fuseaction=home.play&mediaid=A3F4AE5D□B21E□8EBB□069B78254ED2E9C4.

Genaidy, A., Sequeira, R., Rinder, M., A-Rehim, A. 2009. Risk analysis and protection measures in a carbon nanofiber manufacturing enterprise: An exploratory investigation. Science of the Total Environment 407: 5825–5838

Hansen, S.F., Larsen, B.H., Olsen, S.I., Baun, A. (2007). Categories and

Hazard Identification Scheme of Nanomaterials. Nanotoxicology, 3, 243-250.

Hansen, S.F., Michelson, E., Kamper, A., Borling, P., Stuer-Lauridsen, F. &

Baun, A. 2008, Categorization framework to aid exposure assessment of nanomaterials in consumer products, Ecotoxicology 17 (5): 438-447

Hansen, S.F. 2009. Regulation and Risk Assessment of Nanomaterials – Too Little, Too Late? (PhD Thesis). Kgs. Lyngby: DTU Environment. Available: http://www2.er.dtu.dk/publications/fulltext/2009/ENV2009-069.pdf [Accessed 17-04-2009].

Hansen, S.F. 2010. Multicriteria mapping of stakeholder preferences in regulating nanotechnology Journal of Nanoparticle Research 12:1959–1970

Hougaard KS, Jackson P, Jensen KA, Sloth JJ, Löschner K, Larsen EH, Birkedal RK, Vibenholt A, Boisen AMZ, Wallin H, Vogel U (2010) Effects of prenatal exposure to surface-coated nanosized titanium dioxide (UV-Titan). Particle Fibre Toxicol 14;7:16.

Höck J., Epprecht T., Hofmann H., Höhner K., Krug H., Lorenz C., Limbach L., Gehr P., Nowack B., Riediker M., Schirmer K., Schmid B., Som C., Stark W., Studer C., Ulrich A., von Götz N., Wengert S., Wick P.: Guidelines on the Precautionary Matrix for Synthetic Nanomaterials. Federal Office of Public Health and Federal Office for the Environment, Berne 2010, Version 2.Available: http://www.bag.admin.ch/themen/chemikalien/00228/00510/05626/index.html?lang=en
(Accessed 17 May 2010)

Industriens Branchearbejdsmiljøråd. 2011. NANOSAFER Nanopartikler i arbejdsmiljøet. Available: http://www.i-bar.dk/NANOSAFER.aspx (Accessed 14-03-2011)

ISO 2008. Nanotechnologies - Terminology and definitions for nano-objects - Nanoparticle, nanofibre and nanoplate. ISO/TS 27687:2008. Geneva: International Organization for Standardization.

Linkov, I., Satterstrom, F.K., Steevens, J., Ferguson, E., Pleus, R.C. 2007. Multi-criteria decision analysis and environmental risk assessment for nanomaterials. Journal of Nanoparticle Research 9:543–554.

Meldrum, M. 1996. Review of Fibre Toxicology (OELs). Health& Safety Executives. Sudbury, Suffolk; Health& Safety Executives (summary available: http://www.asbestos-institute.ca/reviews/hse/hse-sum.html, accessed 08-09-2010)

Nielsen GD, Roursgaard M, Jensen KA, Poulsen, SS, Larsen ST. In vivo biology and toxicology of fullerenes and their derivatives. Basic Clin Pharmacol Toxicol 2008;103(3):197-208

OECD 1992. OECD Guideline for Testing of Chemicals 301 Adopted: 17.07.92 Ready Biodegradability. Available: http://www.oecd-library.org/docserver/download/fulltext/9730101e.pdf?expires=1303986661&id=id&accname=freeContent&checksum=FD9FA7BFD60C66B90BBFA3B5F61B2562 (Accessed 25-04-2011)

OECD 2011. OECD Guidelines for the Testing of Chemicals, Section 3: Degradation and Accumulation. Available: http://www.oecd-ilibrary.org/environment/oecd-guidelines-for-the-testing-of-chemicals-section-3-degradation-and-accumulation_2074577x (Accessed 25-04-2011)

Paik. S.Y., Zalk, D.M., Swuste, P. 2008. Application of a Pilot Control Banding Tool for Risk Level Assessment and Control of Nanoparticle Exposures. Ann. Occup. Hyg. 52(6): 419–428.

RCEP. 2008. Twenty-seventh Report Novel Materials in the Environment: The case of nanotechnology Royal Commission on Environmental Pollution. Norwich: The Stationery Office

Shinohara, N., Nakamishi, J., Gamo, M. 2009. Risk Assessment of Manufactured Nanomaterials – C60. Available: http://www.aist-riss.jp/main/modules/product/nano_rad.html?ml_lang=en (Accessed July 15, 2010)

Stone, V., Hankin, S., Aitken, R., Aschberger, K., Baun, A., Christensen, F., Fernandes, T., Hansen, S.F., Hartmann, N.B., Hutchinson, G., Johnston, H., Micheletti, G., Peters, S., Ross, B., Sokull-Kluettgen, B., Stark, D., Tran, L. 2009. Engineered Nanoparticles: Review of Health and Environmental Safety (ENRHES). Available: http://nmi.jrc.ec.europa.eu/project/ENRHES.htm (Accessed February 1, 2010).

Stuer-Lauridsen, F., Kamper, A., Borling P., Petersen, G.I., Hansen, S.F., Baun, A. 2007. Mapping of products containing nanoparticles or based on nanotechnology, Mapping of Chemical Substances in Consumer Products, No. 81, 2007, Danish EPA. Available: http://www2.mst.dk/common/Udgivramme/Frame.asp?pg=http://www2.mst.dk/Udgiv/publications/2007/978-87-7052-536-7/html/default_eng.htm

Tervonen, T., J. Figueira, J. Steevens, J. Kim, and I. Linkov. (2009). Risk-based classification system of nanomaterials. Journal of Nanoparticle Research 11:757–766

The Danish Working Environment Authority 2002. C.0.1 October 2002 Limit values for substances and materials.
http://www.at.dk/~/media/AT/at/Engelsk-pdf/At-vejledninger/GVlisteUK%20pdf.ashx
(Accessed 25-04-2011)

Tran CL, SM Hankin, B Ross, RJ Aitken, AD Jones, K Donaldson, V Stone, R Tantra, 2008, 'An outline scoping study to determine whether high aspect ratio nanoparticles (HARN) should raise the same concerns as do asbestos fibres', Report on DEFRA project CB0406

Tønning, K., Poulsen, M. 2007. Nanotechnology in the Danish industry - survey on production and application. Environmental Project No. 1206 2007. 2007. Copenhagen: Danish Ministry of the Environment Danish Environmental Protection Agency.

UNEP 2009. Globally Harmonized System of Classification and Labelling of Chemicals (GHS) Third revised edition United Nations, 2009. Available:
http://live.unece.org/trans/danger/publi/ghs/ghs_rev03/03files_e.html
(Accessed 25-04-2011)

Wikipedia 2011. Phagocyte. Avialable:
http://en.wikipedia.org/wiki/Phagocyte#cite_ref-117
(Accessed 25-04-2011)

Zaik, D., Paik, S.Y., Swuste, P. 2009. Evaluating the Control Banding Nanotool: a qualitative risk assessment method for controlling nanoparticle exposures. J Nanopart Res 11:1685-1704.

APPENDIX 1: NanoRiskCat●●●|●● Template

Subject: <<Insert short title here>> produced by <<Company name>>

Nanomaterial description	
Material source or producer:	<< Insert source of the nanomaterial used in the product. This could be the name of primary producer of the nanomaterial, the distributor, etc.>>
Manufacturing process:	<< If known, the process used to manufacture the nanomaterial should be reported here This could e.g. arc method, chemical vapor deposition, etc. >>
Appearance:	<< Describe the visual appearance of the nanomaterial here e.g. black powder, yellow paste, transparent liquid >>
Chemical composition:	<< Insert chemical formula here e.g. C60, TiO2 >>
Physical form/shape:	<< Insert physical form and shape of the nanomaterial e.g. Powder/spherical, paste/tubes >>
Purity:	<< Insert purity of the nanomaterials e.g. 99.5% >>
Size distribution:	<< Insert primary particle size distribution of the nanomatereal subject for the **NanoRiskCat●●●|●●** >>
Solubility:	<< Insert the solubility of the nanomaterial in

	water e.g. 1.3×10^{-11} mg/mL >>
State of aggregation or agglomeration:	<< Insert state of aggregation or agglomeration e.g. 85-140 nm >>
CAS number (if applicable):	<< Insert CAS number if specifically relevant for the nanomaterial in question >>
Product description	
<< Insert a description of the product including chemical composition (w/w%) of the product subject to the **NanoRiskCat** as well as the purpose of adding the nanomaterial and it's function in the product >>	

Applications

<< Insert information on how the product subject to the **NanoRiskCat**●●●|●● should be used, why the product should be used, how often and duration of the product. Any personal protection equipment, precautions and/or rules of conduct should also be inserted here. Possible routes of exposure to humans and the environment should be clearly stated and so should any recommended measures to prevent exposure. If OELs and PEC/PNECs have been established for the product subject to the **NanoRiskCat**●●●|●● these should be listed here as well as the source of these >>

Exposure potential for professional end-users

According to table 4 in chapter 3 of the **NanoRiskCat**●●●|●● guidance document on Criteria for evaluating the exposure profile, the following REACH Use Descriptor Categories are relevant for <<insert product name>>.

REACH Cat.	#	Description	Examples and explanations
PROC	<<Insert number of first relevant PROC >>	<<Insert PROC description>>	<<Insert PROC examples and explanations>>
PC	<<Insert number of first relevant PC >>	<<Insert PC description>>	<<Insert PC examples and explanations>>
FC	<<Insert number of first relevant PC >>	<<Insert FC description>>	<<Insert FC examples and explanations>>

<<Insert the number, description, examples and explanations of the relevant PROCs, PCs and FCs in the table above. Add rows so that each relevant PROC, PC and FC is located in its own row. Number, description and examples and explanation associated with each PROC, PC, and FC can be found in the tables of appendix 3. The color of the PROC, PC and FC in the tables of appendix 3 should also be indicated here by shading the row.>>

Exposures to the professional end-users of <<Insert product name>> are <<Insert statement about the number of potential exposures e.g. “multiple”, “limited”, “minor”, etc.>> and to <<Insert whether exposure is to be expected or not e.g. “be expected”, “not to be expected”,

etc.>>. The main contact zones with <<Insert product name>> are <<Insert main contact zones e.g. “the hands”, “eyes”, etc>>.

<<Insert note about PCs, AC, no intended release and AC, intended release that are not relevant or fall outside the scope of intended uses of the product subject to this report>>

Considering the color-codes of the PROC(s) (<<Insert bullet (Font 12, times new roman)>>), PC(s) (<<Insert bullet (Font 12, times new roman)>>) and FC(s) (<<Insert bullet (Font 12, times new roman)>>), we concluded that the overall

Exposure potential for professional end-users is <<Insert bullet (Font 20, times new roman) with the color that best summarizes the color of the PROC(s), PC(s) and FC(s) in the table above>>

Consumer exposure potential

According to table 4 in chapter 3 of the **NanoRiskCat**●●●|●● guidance document on Criteria for evaluating the exposure profile, the following REACH Use Descriptor Categories are relevant for <<Insert product name>>.

REACH Cat.	**#**	**Description**	**Examples and explanations**
PC	<<Insert number of first relevant PC >>	<<Insert PC description>>	<<Insert PC examples and explanations>>
AC, no intended release	<<Insert number of first AC, no intended release >>	<< Insert description of AC, no intended release >>	<< Insert examples and explanations of AC, no intended release >>
AC, intended release	<<Insert number of first AC, intended release >>	<< Insert description of AC, intended release >>	<<Insert examples and explanations of AC, intended release >>

<<Insert the number, description, examples and explanations of the relevant PCs, AC, no intended and AC, intended release in the table above. Add rows so that each relevant PC, AC, no intended release and AC, intended release is located in it's own row. Number, description and examples and explanation associated with each PC, AC, no intended release and AC, intended release can be found in the tables of appendix 3. The color of the AC, no intended release and AC, intended release in the tables of appendix 3 should also be indicated here by shading the row>>.

Consumer exposure to <<Insert product name>> are <<Insert statement about the number of potential exposures e.g. "multiple", "limited", "minor", etc.>> and to <<Insert whether exposure is to be expected or not e.g. "be expected", "not to be expected", etc.>>. The main contact zones with <<Insert product name>> are <<Insert main contact zones e.g. "the hands", "eyes", etc>>.

<<Insert note about PCs, AC, no intended release and AC, intended release that are not relevant or fall outside the scope of intended uses of the product subject to this report>>

Considering the color-codes of the PC (<<Insert bullet (Font 12, times new roman)>>), AC, no intended release (<<Insert bullet (Font 12, times new roman)>>) and AC, intended release (<<Insert bullet (Font 12, times new roman)>>), we concluded that the overall

Consumer exposure potential is <<Insert bullet (Font 20, times new roman) with the color that best summarizes the color of the PC, AC, no intended release and AC, intended release in the table above>>

Environmental exposure potential

According to table 4 in chapter 3 of the **NanoRiskCat** guidance document on Criteria for evaluating the exposure profile, the following REACH Use Descriptor Categories are relevant for <<Insert product name>>.

REACH Cat.	#	Description	Examples and explanations
PC	<<Insert number of first relevant PC >>	<<Insert description for this PC>>	<<Insert examples and explanations for this PC>>
AC, no intended release	<<Insert number of first relevant AC, no intended release >>	<<Insert description of this AC, no intended release >>	<<Insert examples and explanations for this AC, no intended release >>
AC, intended release	<<Insert number of first relevant AC, intended release >>	<<Insert description of this AC, intended release >>	<<Insert examples and explanations for this AC, intended release >>

<<Insert the number, description, examples and explanations of the relevant AC, no intended release, AC, intended release and ERC in the table above. Add rows so that each relevant AC, no intended release, AC, intended release and ERC is located in it's own row. Number, description and examples and explanation associated with each AC, no intended, AC, intended release and ERC can be found in the tables of appendix 3. The color of the AC, no intended release, AC, intended release and ERC in the tables of appendix 3 should also be indicated here by shading the row>> Environmental exposure to <<Insert product name>> are <<Insert statement about the number of potential exposures e.g. "multiple", "limited", "minor", etc.>> and to <<Insert whether exposure is to be expected or not e.g. "be expected", "not to be expected", etc.>>. The main outlets to the environment are expected to be <<Insert expected fate of nanomaterial in question, e.g. direct into the water recipients and/or indirectly via the STPs into water recipient and soil>>.

<<Insert note about AC, no intended, AC, intended release and ERC that are not relevant or fall outside the scope of intended uses of the product subject to this report>>

Considering the color-codes of the AC, no intended release (<<Insert bullet (Font 12, times new roman)>>), AC, intended release(s) (<<Insert bullet (Font 12, times new roman)>>) and ERC(s) (<<Insert bullet (Font 12, times new roman)>>), we concluded that the overall

Environmental exposure potential is <<Insert bullet (Font 20, times new roman) with the color that best summarizes the color of the AC, no intended release(s) and AC, intended release(s)

and ERC in the table above>>

Literature methodology/sources of information

The following sources of information were used to fill out the **NanoRiskCat** for <<Insert chemical formula as for nanomaterial used in the product subject of this report >>:

1. <<Insert references in bullets for the information that is cited when filling out the information requirements on human health and environment. This can be either scientific reviews published by international, well-recognized and independent scientific experts or primary literature identified through web of science, pubmed or the ICON database on nanomaterial EHS. If the latter, clearly state which database were used and the search terms used>>.

Human hazard profile

1. **HARN: Does the nanomaterial fulfill the HARN paradigm?**

   Answer: <<Insert either "Yes", "Maybe", "No" or "No information">>

   Arguments and explanation: <<Provide argument and explanation for the why/why not the nanomaterial in question does or does not fulfill the HARN paradigm >>

2. **Bulk – "Level A CLP": Is the bulk form of the nanomaterial known to cause or may cause serious damaging effects?**

   Answer: <<Insert either "Yes", "Maybe", "No" or "No information">>

   Arguments and explanation: <<Provide argument and explanation for the why/why not the nanomaterial in question is not known to cause or may cause serious damaging effects>>

3. **Bulk – "Level B CLP": Is the bulk form of the nanomaterial classified for other less adverse effects according to the CLP?**

   Answer: <<Insert either "Yes", "Maybe", "No" or "No information">>

   Arguments and explanation: <<Provide argument and explanation for the why/why not

the nanomaterial in question is not suspected to cause or may cause serious damaging effects>>

4. **Nano – Acute tox: Is the specific nanomaterial known to be acute toxic?**

Answer: <<Insert either "Yes", "Maybe", "No" or "No information">>

Arguments and explanation: <<Provide a short summary of the scientific evidence in regard to acute toxicity and provide references>>

5. **Are there indications that the nanomaterial causes genotoxic-, mutagenic-, carcinogenic-, respiratory-, cardiovascular, neurotoxic or reproductive effects in humans and/or laboratory animals or has organ-specific accumulation been documented?**

Answer: <<Insert either "Yes", "Maybe", "No" or "No information">>

Arguments and explanation:

a. Genotoxicity and mutagenicity: <<Provide a short summary of the scientific evidence in regard to genotoxicity and mutagenicity and provide references>>

b. Respiratory tract toxicity: <<Provide a short summary of the scientific evidence in regard to respiratory toxicology and provide references>>

c. Cardiovascular toxicity: <<Provide a short summary of the scientific evidence in regard to cardio-vascular effects and provide references>>

d. Neurotoxicity: <<Provide a short summary of the scientific evidence in regard to neurotoxicity and provide references>>

e. Reproductive damage:

<<Provide a short summary of the scientific evidence in regard to reproductive damage

and provide references>>

f. Carcinogenicity: <<Provide a short summary of the scientific evidence in regard to carcinogenicity and provide references>>

g. Organ-specific accumulation: <<Provide a short summary of the scientific evidence in regard to organ-specific accumulation and provide references>>

6. Overall evaluation of human hazard

The overall answer to this question is <<Insert either "Yes", "Maybe", "No" or "No information">> based on the following considerations:

1. << Provide a short summary and explain the reasoning in bullets behind the derivation of the overall evaluation >>

We conclude that the color-code that best reflects the human hazard profile of <<nanomaterial used in product subject to this report>> used in <<product name>> is <<Insert bullet (Font 20, times new roman) with the color that best summarizes the evidence provided above>> based on <<Insert the defaults sentences appendix 2, table 2.1 that describes the nature of the evidence that provides that basis for deriving the color code for human health hazard in NanoRiskCat>>

Environment hazard profile

1. **Bulk – "Level 1 CLP": Is the bulk form of the nanomaterial classified as CLP Acute 1 or Chronic 1 or Chronic 2?**

   Answer: <<Insert either "Yes", "Maybe", "No" or "No information">>

   Arguments and explanation: <<Provide argument and explanation for the why/why not the nanomaterial in question is classified as CLP Acute 1 or Chronic 1 or Chronic 2>>

2. **Nano – LC_{50}<10 mg/l: Is the nanomaterial in question reported to be hazardous to environmental species i.e. LC50 or EC 50 <10 mg/l?**

   Answer: <<Insert either "Yes", "Maybe", "No" or "No information">>

   Argument and explanation: <<Provide a short summary of the scientific evidence in regard to environmental hazards that have established reported LC50 or EC50 on various species after exposure to the nanomaterials subject to the NRC>>

3. **Bulk – "Level 2 CLP": Is the bulk form of the nanomaterial classified as CLP Chonic 3 or Chronic 4 or documented nano-specific effects?**

   Answer: <<Insert either "Yes", "Maybe", "No" or "No information">>

   Arguments and explanation: <<Provide argument and explanation for the why/why not the nanomaterial in question is not classified as CLP Chronic 3 or Chronic 4 or does not cause significant effects for which EC50 or LC50 values cannot be established or non-standardized endpoints have been applied>>

4. **Nano – LC_{50}<100 mg/l: Is the nanomaterial in question reported to be hazardous to environmental species i.e. LC50 or EC 50 <10 mg/l?**

   Answer: <<Insert either "Yes", "Maybe", "No" or "No information">>

   Argument and explanation: <<Provide a short summary of the scientific evidence in regard to environmental hazards that have established reported LC50 or EC50 on various species after exposure to the nanomaterials subject to the NRC>>

5. **$T_{½}$>40 days: Is the nanomaterial in question persistent i.e. T½>40 days?**

   Answer: <<Insert either "Yes", "Maybe", "No" or "No information">>

Argument and explanation: <<Provide argument and explanation for the why/why not the nanomaterial in question is or is not persistent and provide references>>

6. **BCF>50: Is the nanomaterial in question bioaccumulative i.e. BCF>50?**

   Answer: <<Insert either "Yes", "Maybe", "No" or "No information">>

   Argument and explanation: << Provide argument and explanation for the why/why not the nanomaterial in question does/does not accumulate and provide references >>

7. **Dispersive or long-range transport, ecosystem effects?**

   Answer: <<Insert either "Yes", "Maybe", "No" or "No information">>

   Argument and explanation: <<Provide a short summary of the evidence identified in regard to whether the nanomaterial used in the product subject to this report could lead to irreversible harm to the environment and provide references>>

8. **Is the nanomaterial dispersive?**

   Answer: <<Insert either "Yes", "Maybe", "No" or "No information">>

   Argument and explanation: << Provide argument and explanation for the why/why not the nanomaterial in question is or is not readily dispersed and provide references Provide a short summary of the scientific evidence in regard >>

9. **Novelty**

   Answer: <<Insert either "Yes", "Maybe", "No" or "No information">>

   Argument and explanation: << Provide arguments and explain to which extend humans and environment have previously been exposed to the nanomaterials subject to the NRC

10. **Overall evaluation of environmental hazard**

We conclude that the color-code that best reflects the environmental hazard profile of <<nanomaterial used in product subject to this report>> used in <<product name>> is <<Insert bullet (Font 20, times new roman) with the color that best summarizes the evidence provided above>> based on <<Insert the defaults sentences in appendix 2, table 2.2 that describes the nature of the evidence that provides that basis for deriving the color

code for environmental hazard in NanoRiskCat>>

Summary

This information provided and summarized in this template is considered to be accurate at the date of printing and is believed to be a complete reflection of what the <<Insert company name>> knows about the risks of using <<chemical formula of the nanomaterials used in the product subject to this report>> to <<function of the nanomaterial in the product subject to the report>> of <<product name>>.

Exposure			Effects	
Prof	**Consum**	**Environ**	**Human**	**Environ**
<Insert colored bullet for prof exp>	<Insert colored bullet for con exp>	<Insert colored bullet for env exp>	<Insert Colored bullet for hum haz>	<Insert Colored bullet for env haz>
			<< Insert standard sentence number>>[a)]	<< Insert standard sentence number>>[b)]

Red, yellow and green indicate high, medium and low indication of exposure/effect level whereas gray indicates too limited data to assess exposure/effect; a) see Appendix 2, Table A2.1; b) see Appendix 2, Table A2.2.

The overall **NanoRiskCat**code for the <<insert chemical formula of nanomaterial>> in <<product name>> is <<provide list of colored bullet reflecting the conclusions made about exposure potential for professional end-users, consumers, and the environment as well as the conclusions made about the human and environmental hazard profiles>>

NanoRiskCat does not lead directly to a decision, but provides a basis for decision-making by defining a number of concrete criteria that defines to which extend there are indication of exposures and effects for professional users, consumers, and the environment

It is the reader's obligation to evaluate this **NanoRiskCat** in the light of any new scientific evidence regarding risks published after the data of printing and to comply with all applicable laws and regulations.

Date of printing	**Signature**
…<<Insert date/month/year>>**……**	**……**<<Signature of company rep.>>**…**

APPENDIX 2. Additional sentences to explain the color codes in NanoRiskCat.

Table A2.1 Additional sentences to explain the color code for human health hazard in NanoRiskCat.

Sentence no.	Color	Description
1	Red	"based evidence of HARN"
2	Red	"based on bulk CLP classification 1-4 for acute toxicity"
3	Red	"based on CLP classification 1 for skin corrosion/irritation, eye damage/irritation/respiratory and skin sentization"
4	Red	"based on bulk CLP classification 1 or 2 germ cell mutagenicity/carcinogenicity, reproductive toxicity, specific target organ toxicity
5	Red	"based on bulk CLP classification 1 for aspiration toxicity"
6	Red	"based on nano acute tox"
7	Red	a. "based on *in vivo* evidence of effects when testing the nanomaterial (genotox/mutagenicity, respiratory effects, cardio-vascular effects, acute neurotoxic effects, reproductive damage, carcinogenicity, organ accumulation)
		b. "based on *in vivo* evidence of a combination of hazards from testing of the nanomaterial"
8	Red	a. "based on *in vitro* evidence of effects when testing the nanomaterial (genotox/mutagenicity, respiratory effects, cardio-vascular effects, acute neurotoxic effects, reproductive damage, carcinogenicity, organ accumulation)
		b. "based on *in vitro* evidence of a combination of hazards from testing of the nanomaterial"
9	Red	"based on bulk classified as a CLP category 2 in regard to skin corrosion/irritation/ serious eye damage/irritation as well as *in vivo* evidence of hazards from testing of the nanomaterial"
10	Red	"based on bulk classified as a CLP category 3 in regard to specific target organ toxicity - single exposure as well as *in vivo* evidence of hazards from testing of the nanomaterial"
11	Red	"based on bulk classified as a CLP category 2 in regard to skin corrosion/irritation/ serious eye damage/irritation as well as *in vitro* evidence of hazards from testing of the nanomaterial"
12	Red	"based on bulk classified as a CLP category 3 in regard to specific target organ toxicity - single exposure as well as *in vitro* evidence of hazards from testing of the nanomaterial"
13	Yellow	"based on *in vivo* evidence indicating at least one hazard from testing of the nanomaterial"
14	Yellow	"based on *in vitro* evidence indicating at least one hazard from testing of the nanomaterial"
15	Yellow	"based on bulk classified as a CLP category 2 in regard to skin corrosion/irritation/ serious eye damage/irritation as well as evidence of no hazards from testing of the nanomaterial"
16	Yellow	"based on bulk classified as a CLP category 3 in regard to specific target organ toxicity - single exposure as well as evidence of no hazards from testing of the nanomaterial"
17	Yellow	"based on bulk classified as a CLP category 2 in regard to skin corrosion/irritation/ serious eye damage/irritation as well as not enough data on possible hazards from testing of the nanomaterial"
18	Yellow	" based on bulk classified as a CLP category 3 in regard to specific target organ toxicity - single exposure as well as not enough data on possible hazards from testing of the nanomaterial"
19	Grey	"based on not enough *in vitro* and/or *in vivo* data being available on hazards from testing of the nanomaterial"

Table A2.2 Additional sentences to explain the color code for environmental effects in NanoRiskCat.

Sentence no.	Color	Description
1	Red	"based on bulk CLP classification of Acute 1 or Chronic 1 or Chronic 2"
2	Red	"based on nanospecific LC50 or EC50 < 10 mg/l"
3	Red	"based on possible or confirmative evidence of nanospecific LC50 or EC50 < 100 mg/l and T1/2 > 40 d"
4	Red	"based on possible or confirmative evidence of nanospecific LC50 or EC50 < 100 mg/l and BCF > 50"
5	Red	"based on evidence of T1/2 > 40 d and a BCF > 50"
6	Red	a. "based on bulk CLP classification of Chronic 3 or Chronic 4 and nanospecific effects (LC50/EC50 < 100 mg/l or T½>40d or BCF>50)
		b. "based on bulk CLP classification of Chronic 3 or Chronic 4 and T1/2 > 40 d and a BCF > 50"
		c. "based on bulk CLP classification of Chronic 3 or Chronic 4 and an evaluation of dispersive or long range transport, ecosystem effects and novelty"
8	Yellow	"based on a BCF > 50"
9	Yellow	"based on an evaluation of dispersive or long range transport, ecosystem effects and novelty"
10	Yellow	"based on bulk CLP classification of Chronic 3 or Chronic 4 and an evaluation of dispersive or long range transport, ecosystem effects and novelty"
11	Grey	"based on an evaluation of dispersive or long range transport, ecosystem effects and novelty"
12	Grey	"based on bulk CLP classification of Chronic 3 or Chronic 4 and an evaluation of dispersive or long range transport, ecosystem effects and novelty"

APPENDIX 3. Default colors assigned to REACH Use Descriptor Categories

Table 3.1 Default colors assigned to Process categories [PROC]

	Process categories	Examples and explanations
PROC1	Use in closed process, no likelihood of exposure	Use of the substances in high integrity contained system where little potential exists for exposures, e.g. any sampling via closed loop systems
PROC2	Use in closed, continuous process with occasional controlled exposure	Continuous process but where the design philosophy is not specifically aimed at minimizing emissions It is not high integrity and occasional expose will arise e.g. through maintenance, sampling and equipment breakages
PROC3	Use in closed batch process (synthesis or formulation)	Batch manufacture of a chemical or formulation where the predominant handling is in a contained manner, e.g. through enclosed transfers, but where some opportunity for contact with chemicals occurs, e.g. through sampling
PROC4	Use in batch and other process (synthesis) where opportunity for exposure arises	Use in batch manufacture of a chemical where significant opportunity for exposure arises, e.g. during charging, sampling or discharge of material, and when the nature of the design is likely to result in exposure
PROC5	Mixing or blending in batch processes for formulation of preparations* and articles (multistage and/or significant contact)	Manufacture or formulation of chemical products or articles using technologies related to mixing and blending of solid or liquid materials, and where the process is in stages and provides the opportunity for significant contact at any stage
PROC6	Calendering operations	Processing of product matrix Calendering at elevated temperature an large exposed surface
PROC7	Industrial spraying	Air dispersive techniques Spraying for surface coating, adhesives, polishes/cleaners, air care products, sandblasting Substances can be inhaled as aerosols. The energy of the aerosol particles may require advanced exposure controls; in case of coating, overspray may lead to waste water and waste.
PROC8a	Transfer of substance or preparation (charging/ discharging) from/to vessels/large containers at non-dedicated facilities	Sampling, loading, filling, transfer, dumping, bagging in non-dedicated facilities. Exposure related to dust, vapour, aerosols or spillage, and cleaning of equipment to be expected.
PROC8b	Transfer of substance or preparation (charging/discharging) from/to vessels/large containers at dedicated facilities	Sampling, loading, filling, transfer, dumping, bagging in dedicated facilities. Exposure related to dust, vapour, aerosols or spillage, and cleaning of equipment to be expected.

PROC9	Transfer of substance or preparation into small containers (dedicated filling line, including weighing)	Filling lines specifically designed to both capture vapour and aerosol emissions and _tomizat spillage
PROC10	Roller application or brushing	Low energy spreading of e.g. coatings Including cleaning of surfaces. Substance can be inhaled as vapours, skin contact can occur through droplets, splashes, working with wipes and handling of treated surfaces.
PROC11	Non industrial spraying	Air dispersive techniques Spraying for surface coating, adhesives, polishes/cleaners, air care products, sandblasting Substances can be inhaled as aerosols. The energy of the aerosol particles may require advanced exposure controls.
PROC12	Use of blowing agents in manufacture of foam	
PROC13	Treatment of articles by dipping and pouring	Immersion operations Treatment of articles by dipping, pouring, immersing, soaking, washing out or washing in substances; including cold formation or resin type matrix. Includes handling of treated objects (e.g. after dying, plating,). Substance is applied to a surface by low energy techniques such as dipping the article into a bath or pouring a preparation onto a surface.
PROC14	Production of preparations* or articles by tabletting, compression, extrusion, pelletisation	Processing of preparations and/or substances (liquid and solid) into preparations or articles. Substances in the chemical matrix may be exposed to elevated mechanical and/or thermal energy conditions. Exposure is predominantly related to volatiles and/or generated fumes, dust may be formed as well.
PROC15	Use as laboratory reagent	Use of substances at small scale laboratory (< 1 l or 1 kg present at workplace). Larger laboratories and R+D installations should be treated as industrial processes.
PROC16	Using material as fuel sources, limited exposure to unburned product to be expected	Covers the use of material as fuel sources (including additives) where limited exposure to the product in its unburned form is expected. Does not cover exposure as a consequence of spillage or combustion.
PROC17	Lubrication at high energy conditions and in partly open process	Lubrication at high energy conditions (temperature, friction) between moving parts and substance; significant part of process is open to workers. The metal working fluid may form aerosols or fumes due to rapidly moving metal parts.
PROC18	Greasing at high energy conditions	Use as lubricant where significant energy or temperature is applied between the substance and the moving parts

PROC19	Hand-mixing with intimate contact and only PPE available	Addresses occupations where intimate and intentional contact with substances occurs without any specific exposure controls other than PPE.
PROC20	Heat and pressure transfer fluids in dispersive, professional use but closed systems	Motor and engine oils, brake fluids Also in these applications, the lubricant may be exposed to high energy conditions and chemical reactions may take place during use. Exhausted fluids need to be disposed of as waste. Repair and maintenance may lead to skin contact
PROC21	Low energy manipulation of substances bound in materials and/or articles	Manual cutting, cold rolling or assembly/disassembly of material/article (including metals in massive form), possibly resulting in the release of fibres, metal fumes or dust
PROC22	Potentially closed processing operations with minerals/metals at elevated temperature Industrial setting	Activities at smelters, furnaces, refineries, coke ovens. Exposure related to dust and fumes to be expected. Emission from direct cooling may be relevant.
PROC23	Open processing and transfer operations with minerals/metals at elevated temperature	Sand and die casting, tapping and casting melted solids, drossing of melted solids, hot dip _tomization, raking of melted solids in paving Exposure related to dust and fumes to be expected
PROC24	High (mechanical) energy work-up of substances bound in materials and/or articles	Substantial thermal or kinetic energy applied to substance (including metals in massive form) by hot rolling/forming, grinding, mechanical cutting, drilling or sanding. Exposure is predominantly expected to be to dust. Dust or aerosol emission as result of direct cooling may be expected.
PROC25	Other hot work operations with metals	Welding, soldering, gouging, brazing, flame cutting Exposure is predominantly expected to fumes and gases.
PROC26	Handling of solid inorganic substances at ambient temperature	Transfer and handling of ores, concentrates, raw metal oxides and scrap; packaging, unpackaging, mixing/blending and weighing of metal powders or other minerals23
PROC27a	Production of metal powders (hot processes)	Production of metal powders by hot metallurgical processes (_tomization, dry dispersion)24
PROC27b	Production of metal powders (wet processes)	Production of metal powders by wet metallurgical processes (electrolysis, wet dispersion)25

Table 3.2 Default colors assigned to Chemical Product Category (PC)

	Category for describing market sectors (at supply level) regarding all uses (workers and consumers)	**Examples and explanations**	Location of nanoelement		Ref
PC1	Adhesives, sealants		Suspended in liquids (IIIb)		http://www.nanotechproject.org/inventories/consumer/browse/products/6806/ http://www.nanotechproject.org/inventories/consumer/browse/products/nano_glue/
PC2	Adsorbents		Surface bound (IIIa)		http://www.nanotechproject.org/inventories/consumer/browse/products/geohumus_soil_wetting_agent/ http://en.wikipedia.org/wiki/Adsorption#Adsorbents http://nanopatentsandinnovations.blogspot.com/2010/01/honeywelluop-reveal-nano-adsorbents.html
PC3	Air care products		Airborne (IIId)		http://www.healthycleaning101.org/english/ACP_pub.html
PC4	Anti-Freeze and de-icing products		Suspended in liquids (IIIb)	Airborne (IIId)	http://www.nanotechproject.org/inventories/consumer/browse/products/nano_car_sealing_rims_9/ http://www.nauticexpo.com/prod/star-brite/anti-freeze-coolant-additive-21539-49549.html www.cryotech.com/products/runway.php
PC7	Base metals and alloys		Suspended in solid (IIIc)		http://www.nanotechproject.org/inventories/consumer/search/?keywords=disinfectant&company=0&country_origin=0&categories=0&subcategories=0&created=&modifie

					d=&search=1
PC8	Biocidal products (e.g. Disinfectants, pest control)	PC 35 should be assigned to disinfectants being used as a component in a cleaning product	Surface bound (IIIa)	Suspended in liquids (IIIb)	http://www.nanotechproject.org/inventories/consumer/search/?keywords=paint&company=0&country_origin=0&categories=0&subcategories=0&created=&modified=&search=1
PC9a	Coatings and paints, thinners, paint removers		Suspended in liquids (IIIb)		
PC9b	Fillers, putties, plasters, modelling clay		Suspended in liquids (IIIb)		
PC9c	Finger paints		Suspended in liquids (IIIb)		http://www.911review.com/energeticmaterials09/videnskab/DanishScientist.html
PC11	Explosives		Suspended in liquids (IIIb)		http://www.agronano.com/nanogro.htm http://www.alibaba.com/product-free/107088915/Iron_Chelate_Fertilizer_nano_technology_.html
PC12	Fertilizers		Suspended in liquids (IIIb)		http://www.nanotechproject.org/inventories/consumer/browse/products/4970/ http://www.nanotechproject.org/inventories/consumer/browse/products/nanotech_eefuel_additive/
PC13	Fuels		Suspended in liquids (IIIb)		
PC14	Metal surface treatment products, including galvanic and electroplating products	This covers substances permanently binding with the metal surface	Suspended in liquids (IIIb)	Surface bound (IIIa)	
PC15	Non-metal-surface treatment products	Like for example treatment of walls before painting.	Suspended in liquids (IIIb)	Surface bound (IIIa)	http://www.sciencedirect.com/science?_ob=ArticleURL&_udi=B6V1Y-4JTRTK7-3&_user=10&_coverDate=12%2F31%2F2006&_rdoc=1&_fmt=high&_orig=search&_sort=d&_docanchor=&view=c&_searchStrId=1343317079&_rerunOrigin=google&_acct=C

					000050221&_version=1&_urlVersion=0&_userid=10&md5=6978691d9c52dda8248bbe48b9a6c954 http://www.waxmelters.com/Melt-Wax-Faster-with-your-Water-Jacketed-Melter-s/82.htm
PC16	Heat transfer fluids		Suspended in liquids (IIIb)		http://www.wikipatents.com/US-Patent-7377176/nano-particle-modified-fill-fluid-for-pressure-transmitters
PC17	Hydraulic fluids		Suspended in liquids (IIIb)		http://www.nanotechproject.org/inventories/consumer/search/?keywords=ink&company=0&country_origin=0&categories=0&subcategories=0&created=&modified=&search=1
PC18	Ink and toners		Suspended in liquids (IIIb)		
PC19	Intermediate				
PC20	Products such as ph-regulators, flocculants, precipitants, neutralization agents	This category covers processing aids used in the chemical industry	Suspended in liquids (IIIb)		
PC21	Laboratory chemicals		Suspended in liquids (IIIb)	Airborne (IIId)	http://www.nanotechproject.org/inventories/consumer/search/?keywords=impregnation&company=0&country_origin=0&categories=0&subcategories=0&created=&modified=&search=1
PC23	Leather tanning, dye, finishing, impregnation and care products		Suspended in liquids (IIIb)		http://www.nanotechproject.org/inventories/consumer/browse/products/5170/
PC24	Lubricants, greases, release products		Suspended in liquids (IIIb)		
PC25	Metal working fluids		Suspended in liquids (IIIb)		

PC26	Paper and board dye, finishing and impregnation products: including bleaches and other processing aids		Suspended in liquids (IIIb)		http://www.nanotechproject.org/inventories/consumer/browse/products/7108/
PC27	Plant protection products		Suspended in liquids (IIIb)		
PC28	Perfumes, fragrances		Suspended in liquids (IIIb)	Airborne (IIId)	
PC29	Pharmaceuticals		Suspended in liquids (IIIb)		
PC30	Photo-chemicals		Suspended in liquids (IIIb)		http://www.nanotechproject.org/inventories/consumer/search/?keywords=wax&company=0&country_origin=0&categories=0&subcategories=0&created=&modified=&search=1 http://www.nanotechproject.org/inventories/consumer/search/?keywords=polish&company=0&country_origin=0&categories=0&subcategories=0&created=&modified=&search=1
PC31	Polishes and wax blends		Suspended in liquids (IIIb)		http://www.sciencedirect.com/science?_ob=ArticleURL&_udi=B6TH1-4X1YCFX-6&_user=10&_coverDate=02%2F01%2F2010&_rdoc=1&_fmt=high&_orig=search&_sort=d&_docanchor=&view=c&_searchStrId=1343350524&_rerunOrigin=google&_acct=C000050221&_version=1&_urlVersion=0&_userid=10&md5=703a6346fcb098d5a9d1f4f395e5fd97 http://www.imm.ac.cn/journal/ccl/1511/151124-1342-03-0827-p3.pdf
PC32	Polymer preparations and		Suspended in	Suspended in	http://www.nanotechproject.org/inventories/consumer/browse/products/amd_athlo

	compounds		liquids (IIIb)	solid (IIIc)	n_64_fx_processor/ http://www3.interscience.wiley.com/journal/106582703/abstract?CRETRY=1&SRETRY=0
PC33	Semiconductors		Structured surface (IIa)	Suspended in liquids (IIIb)	
PC34	Textile dyes, finishing and impregnating products; including bleaches and other processing aids		Suspended in liquids (IIIb)		http://www.nanotechproject.org/inventories/consumer/search/?search=1&keywords=washing
PC35	Washing and cleaning products (including solvent based products)		Surface bound (IIIa)	Suspended in liquids (IIIb)	http://www.magneticwatersystems.com/custom-water-filters.html
PC36	Water softeners		Suspended in liquids (IIIb)	Airborne (IIId)	
PC37	Water treatment chemicals		Suspended in liquids (IIIb)		
PC38	Welding and soldering products (with flux coatings or flux cores.), flux products		Suspended in solid (IIIc)	Bulk (Ia)	
PC39	Cosmetics, personal care products		Surface bound (IIIa)	Suspended in liquids (IIIb)	
PC40	Extraction agents		Suspended in liquids (IIIb)	Airborne (IIId)	
PC0	Other (UCN codes: see last row)				
Other (use UCN codes: see last row)					

http://www.rivm.nl/en/healthanddisease/productsafety/ConsExpo.jsp

http://195.215.251.229/fmi/xsl/spin/SPIN/guide/menuguide.xsl?-db=spinguide&-lay=overview&-view#

Table 3.3 Default colors assigned to technical functions a substance may have in a chemical product (preparation*) or article

	Function	Explanation	Location of the nanoelement
1	Aerosol propellants	Compressed or liquefied gases within which substances are dissolved or suspended and expelled from a container upon discharge of the internal pressure through expansion of the gas	Suspended in liquid (IIIb); Airborne (IIId)
2	Agents adsorbing and absorbing gases or liquids	Substances used to absorb or adsorb gases or liquids: filter materials/media; molecular sieves; silica gel, etc.	Suspended in liquids (IIIb), Bulk (IIb), Surface bound (IIIa)
3	Anti-condensation agents	Substances used to avoid condensation on surfaces and in the atmosphere: anti-dim agents; condensation removers	Surface bound (IIIa)
4	Anti-freezing agents	Substances used to prevent and remove ice formation: antifreeze liquids; deicing agents	Suspended in liquids (IIIb), Airborne (IIId)
5	Anti-set off and adhe-sive agents	Substances used to prevent set-off and adhesion: spraying powder and anti-set-off additives for printing; oils and waxes for laths and shuttering; casting slip, etc.	Suspended in liquids (IIIb), Airborne (IIId)
6	Anti-static agents	Substances used to prevent or reduce the tendency to accumulate electrostatic charges: anti-static additives; substances for surface treatment against static	Surface bound (IIIa)

		electricity	
7	Binding agents	Resin or polymer-substances in coatings and adhesives	Suspended in liquids (IIIb)
8	Biocide substances		Suspended in liquids (IIIb), Airborne (IIId)
9	Bleaching agents	Substances used to whiten or decolourise materials. Not: cosmetics; photographic bleaches; optical brighteners.	Suspended in liquids (IIIb)
10a	Colouring agents, dyes		Suspended in liquids (IIIb)
10b	Colouring agents, pigments		Suspended in liquids (IIIb); Powders
11	Complexing agents	Substances used to combine with other substances (mainly metal ions) to form complexes	Suspended in liquids (IIIb), Powders
12	Conductive agents	Substances used to conduct electrical current. Sub-categories electrolytes; electrode materials.	Suspended in liquids (IIIb), Bulk (IIb), Powders
13	Corrosion inhibitors and anti-scaling agents	Substances used to prevent corrosion: corrosion inhibiting additives; rust preventives	Suspended in liquids (IIIb), Airborne (IIId)
14	Dust binding agents	Substances used to control finely divided solid particles of powdered or ground materials to reduce their discharge into	Suspended in liquids (IIIb), Powders

		the air		
15	Explosives	Suspended in liquids (IIIb)		
16	Fertilisers	Suspended in liquids (IIIb); Powder		
17	Fillers	Relatively inert, and normally non-fibrous, finely divided substances added to elastomers, plastics, paints, ceramics, etc., usually to extend volume	Suspended in liquids (IIIb); Suspended in a solid (IIIc)	
18	Fixing agents	Substances used to interact with a dye on fibres to improve fastness	Suspended in liquids (IIIb)	
19	Flame retardants	Substances incorporated into, or applied to the surface of, materials to slow down or prevent combustion	Surface bound (IIIa)	
20	Flotation agents	Substances used to concentrate and obtain minerals from ores: flotation oil; flotation, depressants	Suspended in liquids (IIIb)	
21	Flux agents for casting	Substances used to promote the fusing of minerals or prevent oxide formation	Suspended in liquids (IIIb), Powders	
22	Foaming (blowing) agents	Substances used to form a foam or cellular structure in a plastic or rubber material: physically by expansion of compressed gases or vaporisation of liquid, or chemically by decomposition evolving a gas	Suspended in liquids (IIIb)	Suspended in a solid (IIIc)
23	Food/feedstuff additives		Suspended in liquids (IIIb), Powders	
24	Fuels and fuel additives		Suspended in liquids (IIIb)	
25	Heat transfer agaents		Suspended in liquids (IIIb), Powders	
26	Impregnation agents	Substances used to admix with solid materials, which retain their original form: impregnating agents for leather, paper, textile and wood. Not: flame retardants; conserving agents; biocides.	Suspended in liquids (IIIb	

27	Intermediates			
28	Laboratory chemicals	Substances used in laboratories for analytical purposes	Suspended in liquids (IIIb), Powders	
29	Lubricants and lubricant additives	Substances entrained between two surfaces and thereby used to reduce friction: oils; fats; waxes; friction reducing additives	Suspended in liquids (IIIb	
30	Odour agents	Substances used to produce, enhance or mask odour. Not: food additives; cosmetics.	Suspended in liquids (IIIb)	
31	Oxidizing agents	Substances that give up oxygen easily, remove hydrogen from other sub-stances, or accept electrons in chemical reactions, and are used for such purposes	Suspended in liquids (IIIb), Powders	Bulk (IIb)
32	Pharmaceutical substance		Suspended in liquids (IIIb)	
33	Photosensitive agents and other photo-chemicals	Substances used to create a permanent photographic image. Sub-categories: desensitisers; developers; fixing agents; photosensitive agents; sensitizers; anti-fogging agents; light stabilisers; intensifiers.	Suspended in liquids (IIIb)	
34	pH-regulating agents		Suspended in liquids (IIIb); Powders	
35	Plant protection active substance		Suspended in liquids (IIIb); Powders	
36	Plating agents and metal surface treating agents		Suspended in liquids (IIIb)	
37	Pressure transfer agents		Suspended in liquids (IIIb), Powders	Bulk (IIb)
38	Process regulators, other than polymerization or vulcanization processes	Substances used to regulate the speed of a (chemical) process, e.g. accelerators; activators; catalysts; inhibitors; siccatives; anti-siccatives; cross-linking	Suspended in liquids (IIIb), Powders	Surface bound (IIIa)

		agents; initiators; photo-initiators, etc.		
39	Process regulators, used in vulcanization or polymerization processes	Substances used to regulate the speed of a (chemical) process, e.g. accelerators; activators; catalysts; inhibitors; siccatives; anti-siccatives; Cross-linking agents; initiators; photo-initiators, etc.	Suspended in liquids (IIIb), Powders	Surface bound (IIIa)
40	Processing aid, not otherwise listed			
41	Reducing agents	Substances used to remove oxygen, hydrogenate or, in general, act as electron donors in chemical reactions	Suspended in liquids (IIIb), Powders	Surface bound (IIIa)
42	Reprographic agents (Toners)	Substances used to reproduce a permanent image	Suspended in liquids (IIIb)	Bulk (Ib)
43	Semiconductors and photovoltaic agents	Substances having resistivities that are between those of insulators and metals, and are usually changeable by light, heat or electrical or magnetic field, or generate electromotive force upon the incidence of radiant energy	Suspended in liquids (IIIb)	Bulk (Ib)
44	Softeners	Substances used for softening materials to improve feel, to facilitate finishing processes or to impart flexibility or workability. Sub-categories: coalescing agents; bates (leather technology); de-vulcanising agents; emollients; swelling agents; water softeners; plasticisers.	Suspended in liquids (IIIb)	
45	Solvents	Substances used to dissolve, thin, dilute and extract: extraction agents; solvents and thinners for paints, lacquers, adhesives and other materials	Suspended in liquids (IIIb)	

46	Stabilisers	Substances used to prevent or slow down spontaneous changes in, and aging of, materials	Suspended in liquids (IIIb);	Suspended in solid (IIIc)
47	Surface active agents	Substances used to lower the surface and/or interfacial tension of liquids and promote cleaning, wetting, dispersion, etc.	Suspended in liquids (IIIb), Powders	
48	Tanning agents	Substances used for treating hides and skins	Suspended in liquids (IIIb)	
49	Viscosity adjustors	Substances used to modify the flow characteristics of other substances, or preparations, to which they are added	Suspended in liquids (IIIb); Powder	
50	Other			

Table 3.4 Default colors assigned to Article categories, no release intended (AC)

	Article categories (and non exhaustive examples) for describing the type of article in which the substance is contained during service life and waste life	Suitable TARIC chapters	Location of the nanoelement	
Categories of complex articles				
AC1	Vehicles	86-89	Suspended in solid (IIIc)	
	Examples: Trucks, passenger cars and motor cycles, bicycles, tricycles and associated transport equipment; other vehicles: Railway, aircraft, vessels, boats			
AC2	Machinery, mechanical appliances, electrical/electronic articles	84/85	Suspended in solid (IIIc)	
	Examples: Machinery and mechanical appliances; electrical and electronic articles, e.g. computers, video and audio recording, communication equipment; lamps and lightening; cameras; refrigerator, dish washer, washing machines			
AC3	Electrical batteries and accumulators	8506/07	Suspended in solid (IIIc)	Suspended in liquids (IIIb
Categories of material based articles				
AC4	Stone, plaster, cement, glass and ceramic articles	68/69/70	Suspended in solid (IIIc)	
	Examples: Glass and ceramic article: e.g. dinner ware, drinking glasses, pots, pans, food storage containers; construction and isolation articles; natural or artificial abrasive powder or grain, on a base of textile material, of paper, of paperboard or of other materials			
AC5	Fabrics, textiles and apparel	50-63, 94/95	Surface bound (IIIa)	
	Examples: Clothing, bedding, mattress, curtains, upholstery, carpeting/flooring, car seats, textile toys			
AC6	Leather articles	41-42, 64, 94	Surface bound (IIIa)	Suspended in solid (IIIc)
	Examples: Cutlery, cooking utensils, pots, pans, jewellery, toys, furniture, construction articles			
AC8	Paper articles	48-49	Surface bound (IIIa)	Suspended in solid (IIIc)

	Examples: Paper articles: tissue, towels, disposable dinnerware, nappies, feminine hygiene products, adult incontinence products; paper articles for writing, office pa-per; printed paper articles: e.g. newspapers, books, magazines, printed photo-graphs; wallpaper			
AC10	Rubber articles	40, 64, 95	Surface bound (IIIa)	Suspended in solid (IIIc)
	Examples: Tyres, flooring, gloves, footwear, toys			
AC11	Wood articles	44, 94/95	Surface bound (IIIa)	Suspended in solid (IIIc)
	Examples: Flooring, walls, furniture, toys, construction articles			
AC13	Plastic articles	39, 94/95, 85/86	Surface bound (IIIa)	Suspended in solid (IIIc)
	Examples: Plastic dinner ware, food storage, food packaging, baby bottles; flooring, toys, furniture, small plastic articles of daily use e.g. ball pen, PC, mobile phone construction articles			
Other (use TARIC codes: see last row)				
http://ec.europa.eu/taxation_customs/dds/tarhome_en.htm				

Please note: This list is not complete with regard to uses potentially to be described under REACH. Describe other uses as appropriate

Table 3.5 Default colors assigned to Use descriptor for articles with intended release of substances Descriptor based on an indicative list of examples

AC30	Other articles with intended release of substances, please specify26
AC31	Scented clothes
AC32	Scented eraser
AC33	*Entry has been removed after the REACH CA meeting in March 2008*
AC34	Scented Toys
AC35	Scented paper articles
AC36	Scented CD
AC38	Packaging material for metal parts, releasing grease/corrosion inhibitors

Table 3.6 Default colors assigned to Description for Environmental Release Categories (ERC)

ERC	Name	Description	Lifecycle Stage	Level of con-tainment	Intended technical fate of substance	Dispersion of emission sources	Indoor/ outdoor	Release promotion during service life	Location of nanoele ment	Comments
1	Manufa cture of substan ces	Manufacture of organic and inorganic substances in chemical, petrochemical, primary metals and minerals industry including intermediates, monomers using continuous processes or batch processes applying dedicated or multi-purpose equipment, either technically controlled or operated by manual interventions	Manufact ure	Open-closed		Industrial	Indoor	n.a	Suspend ed in liquids (IIIb); Airborne (IIId)	Open-closed indoor industrial manufacturin g of substances might results in environment al exposure
2	Formula tion of prepara tions*	Mixing and blending of substances into (chemical) preparations in all types of formulating	Formulat ion	Open-closed	Not included into matrix	Industrial	Indoor	n.a.	Suspend ed in liquids (IIIb)	Open-closed indoor formulation not included into matrix

		industries, such as paints and do-it-yourself products, pigment paste, fuels, household products (cleaning products), lubricants, etc.								might result in environmental exposure
3	Formulation in materials	Mixing or blending of substances which will be physically or chemically bound into or onto a matrix (material) such as plastics additives in master batches or plastic compounds. For instance a plasticizers or stabilizers in PVC master-batches or products, crystal growth regulator in photographic films, etc.	Formulation	Open-closed	Inclusion into/onto matrix	Industrial	Indoor	n.a.	Surface bound (IIIa); Suspended in solids (IIIc)	
4	Industrial use of processing aids	Industrial use of processing aids in continuous processes or batch processes	End use	Open-closed	Processing aid	Industrial	Indoor	n.a.		

	in processes and products, not becoming part of articles	applying dedicated or multi-purpose equipment, either technically controlled or operated by manual interventions. For example, solvents used in chemical reactions or the 'use' of solvents during the application of paints, lubricants in metal working fluids, anti-set off agents in polymer moulding/casting.								
5	Industrial use resulting in inclusion into or onto a matrix	Industrial use of substances as such or in preparations (non-processing aids), which will be physically or chemically bound into or onto a matrix (material) such as binding agent in paints and coatings or adhesives, dyes in	End use	Open-closed	Inclusion into/onto matrix	Industrial	Indoor	n.a.	Surface bound (IIIa); Suspended in solids (IIIc)	

		textile fabrics and leather products, metals in coatings applied through plating and galvanizing processes. The category covers substances in articles with a particular function and also substances remaining in the article after having been used as processing aid in an earlier life cycle stage (e.g. heat stabilisers in plastic processing).								
6a	Industrial use resulting in manufacture of another substance (use of interme	Use of intermediates in primarily the chemical industry using continuous processes or batch processes applying dedicated or multi-purpose equipment, either technically controlled or operated by manual	End use	Open-closed	Intermediate	Industrial	Indoor	n.a.		

	diates)	interventions, for the synthesis (manufacture) of other substances. For instance the use of chemical building blocks (feedstock) in the synthesis of agrochemicals, pharmaceuticals, monomers, etc.								
6b	Industrial use of reactive processing aids	Industrial use of reactive processing aids in continuous processes or batch processes applying dedicated or multi-purpose equipment, either technically controlled or operated by manual interventions. For example the use of bleaching agents in the paper industry.	End use	Open-closed	Reactive processing aid	Industrial	Indoor	n.a.	Suspended in liquids (IIIb)	
6c	Industrial use of monom	Industrial use of monomers in the production of	End use	Open-closed	Monomers for polymers	Industrial	Indoor	n.a.	Suspended in solids	

	ers for manufacture of thermo plastics	polymers, plastics (thermoplastics), polymerization processes. For example the use of vinyl chloride monomer in the production of PVC.							(IIIc)	
6d	Industrial use of process regulators for polymerisation processes in production of resins, rubbers, polymers	Industrial use of chemicals (cross-linking agents, curing agents) in the production of thermosets and rubbers, polymer processing. For instance the use of styrene in polyester production or vulcanization agents in the production of rubbers.	End use	Open-closed	Monomers for rubbers or thermosets	Industrial	Indoor	n.a.	Suspended in solids (IIIc)	
7	Industrial use of substances in closed systems	Industrial use of substances in closed systems. Use in closed equipment, such as the use of liquids in hydraulic	End use	Closed system	Processing aid	Industrial	Indoor	n.a.	Suspended in liquids (IIIb)	The description of ERC7 states that "low

		systems, cooling liquids in refrigerators and lubricants in engines and dielectric fluids in electric transformers and oil in heat exchangers. No intended contact between functional fluids and products foreseen, and thus low emissions via waste water and waste air to be expected.								emissions via waste water and waste air to be expected.”
8a	Wide dispersive indoor use of processing aids in open systems	Indoor use of processing aids by the public at large or professional use. Use (usually) results in direct release into the environment/sewage system, for example, detergents in fabric washing, machine wash liquids and lavatory cleaners, automotive and bicycle care products (polishes, lubricants, deicers), solvents in paints and adhesives	End use	Open-closed	Processing aid	Wide dispersive	Indoor	n.a.	Suspended in liquids (IIIb)	Open-closed wide dispersive use and the ERC8a description states that: “Use (usually) results in direct release into the environment /sewage system,…”

		or fragrances and aerosol propellants in air fresheners.								
8b	Wide dispersive indoor use of reactive substances in open systems	Indoor use of reactive substances by the public at large or professional use. Use (usually) results in direct release into the environment, for example, sodium hypochlorite in lavatory cleaners, bleaching agents in fabric washing products, hydrogen peroxide in dental care products.	End use	Open-closed	Reaction on use	Wide dispersive	Indoor	n.a.	Suspended in liquids (IIIb)	Open-closed wide dispersive use and the ERC8b description states that "Use (usually) results in direct release into the environment …"
8c	Wide dispersive indoor use resulting in inclusion into or onto a matrix	Indoor use of substances (non-processing aids) by the public at large or professional use, which will be physically or chemically bound into or onto a matrix (material) such as binding agent in paints and coatings or adhesives, dyeing of textile fabrics.	End use	Open-closed	Inclusion into/onto matrix	Wide dispersive	Indoor	n.a.	Surface bound (IIIa); Suspended in solids (IIIc)	Open-closed wide dispersive onto or including into a matrix which indicates limited exposure on the environment

8d	Wide dispersive outdoor use of processing aids in open systems	Outdoor use of processing aids by the public at large or professional use. Use (usually) results in direct release into the environment, for example, automotive and bicycle care products (polishes, lubricants, deicers, detergents), solvents in paints and adhesives.	End use	Open-closed	Processing aid	Wide dispersive	Outdoor	n.a.	Suspended in liquids (IIIb)	Open-closed wide dispersive use and the ERC8b description states that "Use (usually) results in direct release into the environment …"
8e	Wide dispersive outdoor use of reactive substances in open systems	Outdoor use of reactive substances by the public at large or professional use. Use (usually) results in direct release into the environment, for example, the use of sodium hypochlorite or hydrogen peroxide for surface cleaning (building materials)	End use	Open-closed	Reaction on use	Wide dispersive	Outdoor	n.a.	Suspended in liquids (IIIb)	Open-closed wide dispersive use and the ERC8b description states that "Use (usually) results in direct release into the environment …"

8f	Wide dispersive outdoor use resulting in inclusion into or onto a matrix	Outdoor use of substances (non-processing aids) by the public at large or professional use, which will be physically or chemically bound into or onto a matrix (material) such as binding agent in paints and coatings or adhesives.	End use	Open-closed	Inclusion into/onto matrix	Wide dispersive	Outdoor	n.a.	Surface bound (IIIa); Suspended in solids (IIIc)	Open-closed wide dispersive onto or including into a matrix which indicates limited exposure on the environment
9a	Wide dispersive indoor use of substances in closed systems	Indoor use of substances by the public at large or professional (small scale) use in closed systems. Use in closed equipment, such as the use of cooling liquids in refrigerators, oil-based electric heaters.	End use	Closed systems	Processing aid	Wide dispersive	Indoor	n.a.	Suspended in liquids (IIIb)	Indoor use in closed systems indicates the possibility of environmental exposure whereas the widely disperse nature of the use indicates the possibility of environmental potential

9b	Wide dispersive outdoor use of substances in closed systems	Outdoor use of substances by the public at large or professional (small scale) use in closed systems. Use in closed equipment, such as the use of hydraulic liquids in automotive suspension, lubricants in motor oil and break fluids in automotive brake systems.	End use	Closed systems	Processing aid	Wide dispersive	Outdoor	n.a.	Suspended in liquids (IIIb)	Outdoor and widely disperse use by the public at large indicates the possibility of environmental exposure use in a closed equipment indicates the possibility of environmental potential
10a	Wide dispersive outdoor use of long-life articles and materials with low release	Low release of substances included into or onto articles and materials during their service life in outdoor use, such as metal, wooden and plastic construction and building materials (gutters, drains, frames, etc.)	Service life	Open	Inclusion into/onto matrix	Wide dispersive	Outdoor	Low	Surface bound (IIIa); Suspended in solids (IIIc)	Open outdoor wide dispersive onto or including into a matrix indicates some, but limited exposure to the environment

10b	Wide dispersive outdoor use of long-life articles and materials with high or intended release (including abrasive processing)	Substances included into or onto articles and materials with high or intended release during their service life from outdoor use. Such as tyres, treated wooden products, treated textile and fabric like sun blinds and parasols and furniture, zinc anodes in commercial shipping and pleasure craft, and brake pads in trucks or cars. This also includes releases from the article matrix as a result of processing by workers. These are processes typically related to PROC 21, 24, 25, for example: Sanding of buildings (bridges, facades) or vehicles (ships).	Service life	Open	Inclusion into/onto matrix Removing from matrix	Wide dispersive	Outdoor	High	Surface bound (IIIa); Suspended in solids (IIIc)	Open outdoor wide dispersive onto or including into a matrix followed by "Removing from matrix" indicates high levels of exposure to the environment
11a	Wide dispersive indoor use of	Low release of substances included into or onto articles and materials during their service life from	Service life	Open	Inclusion into/onto matrix	Wide dispersive	Indoor	Low	Surface bound (IIIa); Suspend	Open indoor wide dispersive onto or

	long-life articles and materials with low release	indoor use. For example, flooring, furniture, toys, construction materials, curtains, footwear, leather products, paper and cardboard products (magazines, books, news paper and packaging paper), electronic equipment (casing).							ed in solids (IIIc)	including into a matrix indicates some, but limited exposure to the environment
11b	Wide dispersive indoor use of long-life articles and materials with high or intended release (including abrasive processing)	Substances included into or onto articles and materials with high or intended release during their service life from indoor use. For example: release from fabrics, textiles (clothing, floor rugs) during washing. This also includes releases from the article matrix as a result of processing by workers. These are processes typically related to PROC 21, 24, 25. For example removal of indoor paints.	Service life	Open	Inclusion into/onto matrix Removing from matrix	Wide dispersive	Indoor	High	Surface bound (IIIa); Suspended in solids (IIIc)	Open indoor wide dispersive onto or including into a matrix followed by "Removing from matrix" indicates high levels of exposure to the environment

12a	Industrial processing of articles with abrasive techniques (low release)	Substances included into or onto articles and materials are released (intended or not) from the article matrix as a result of processing by workers. These processes are typically related to PROC 21, 24, 25. Processes where the removal of material is intended, but the expected release remains low, include for example: cutting of textile, cutting, machining or grinding of metal or polymers in engineering industries.	Service life	Open-closed	Losses from matrix during article processing	Industrial	Indoor	Low	Surface bound (IIIa); Suspended in solids (IIIc)	Open-closed indoor wide dispersive onto or including into a matrix indicates some, but limited exposure to the environment
12b	Industrial processing of articles with abrasive techniques (high release)	Substances included into or onto articles and materials are released (intended or not) from/with the article matrix as a result of processing by workers. These processes are typically related to PROC 21, 24, 25.	Service life	Open-closed	Losses with matrix during article processing	Industrial	Indoor	High	Surface bound (IIIa); Suspended in solids (IIIc)	Open-closed indoor wide dispersive onto or including into a matrix followed by "Losses with matrix during article

		Processes where the removal of material is intended, and high amounts of dust may be expected, includes for example: sanding operations or paint stripping by shot-blasting.								processing" indicates high levels of exposure to the environment